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Pharmacokinetics and toxicity of two modalities of etoposide infusion in metastatic non-small-cell lung carcinoma*

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Summary. The pharmacokinetics and toxicity of two schedules of etoposide administration were studied in 19 patients suffering from metastatic non-small-cell lung cancer. Ten subjects received a 72-h continuous venous infusion (CVI) of 360 mg/m^2 etoposide, and nine were given a daily dose of 120 mg/m^2 for 3 consecutive days. In the two groups 80 mg/m^2 *cis*-diamminedichloroplatinum (II) (CDDP) was infused on day 1. With CVI, the steady-state plasma concentration was reached 12–24 h after the start of the treatment. The plasma elimination rate showed a biexponential decay curve in both groups. No significant difference between total body clearance and the β-phase volume of distribution was noted between the two modalities of administration. No relationship was found between biological and pharmacokinetic parameters.

Introduction

The antineoplatic agent etoposide (VP16) has demonstrated marked activity in non-small-cell carcinoma of the lung (NSCLC). Its synergistic therapeutic activity with *cis*-diamminedichloroplatinum (II) (CDDP) has been shown in animal models and confirmed in clinical trials [17, 18, 21]. The most widely used schedule of administration is a daily short infusion for 3 consecutive days every 3 weeks [3, 9, 15, 19]. Some pharmacological data tend to suggest that this drug could be properly given by continuous venous infusion (CVI). First, although its mechanism of action has not been totally elucidated, a cell-cycle-specific activity, mainly in phase S or G2, has been demonstrated [16]. Second, the plasma elimination half-life is rather short, ranging from 4 to 8 h [5, 7, 10, 13, 22], suggesting that steady state could be achieved after 24 h of infusion. On these grounds, several authors [1, 4] have conducted phase I trials using 5- or 3-day CVI of VP16, in which hematologic toxicity was dose-limiting.

The present study was undertaken to compare the pharmacokinetic parameters of two modalities of VP16 administration given at the same dose to patients with NSCLC either as a 72-h CVI or as a daily short infusion for 3 consecutive days. Toxicity and clinical response were also assessed in each group and then compared.

Patients and methods

Patients. A total of 19 patients (18 men and 1 women) with untreated, advanced NSCLC (stage III or IV) (10 adenocarcinomas, 8 squamous-cell carcinomas, and 1 undifferentiated carcinoma) consented to enter this study. Eligibility criteria were as follows: an age of <70 years, a creatinine level of <120 μmol/l, a calculated creatinine clearance of >60 ml/min, a bilirubin level of <20 μmol/l, and a performance status of <3 (WHO scale). Patients were randomized into two groups. The first (group A) received a 72-h CVI and comprised ten men (mean age, 59.4±4.3 years). The second (group B) received a daily dose of VP16 for 3 days and consisted of eight men and one woman (mean age, 55±7.1 years).

Treatment plan. The treatment combined CDDP and VP16. CDDP was infused for 1 h at 11 a.m. at a dose of 80 mg/m^2 on day 1, with preceding, simultaneous and subsequent osmotically induced diuresis. In group A, 360 mg/m^2 VP16 was given as a 72-h CVI starting on day 1 at 6 p.m. Group B received 120 mg/m^2 VP16 given as a 60-min infusion on days 1–3 at 6 p.m. Treatment was repeated every 21 days at the same dose.

Evaluation of toxicity and clinical response. Patients underwent weekly determinations of WBC, polymorphonuclear cell, and platelet counts, and serum biochemistries were carried out every 3 weeks. Toxicity was evaluated according to the WHO scale. Side effects noted during the two schedules of administration were compared using the chi-square test. Clinical response was evaluated using Southwest Oncology Group (SWOG) criteria in patients receiving more than two cycles of chemotherapy.

Pharmacokinetic protocol. VP16 pharmacokinetics was evaluated in each patient during the first course of chemotherapy only. Blood samples (5 ml) were collected in dry glass tubes via an indwelling heparin lock that was placed in the arm opposite the perfusion site. After immediate centrifugation, the serum was removed and frozen at –20° C until analysis.

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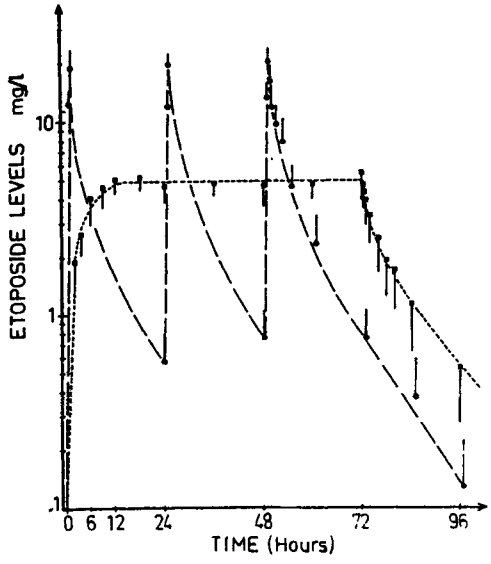

Fig. 1. Plasma concentrations of VP16 as a function of time. ■ – – – ■, schedule A; ● – – – ●, schedule B

Table 1. Comparison of the pharmacokinetic parameters of VP16 after a 72-h CVI (schedule A) and repeated daily i. v. administration (schedule B) of the same dose (360 mg/m²)

Schedule	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Cl (min/ml/m²)	Vdβ (l/m²)	Vd_{ss} (l/m²)	AUC (mg/l/h)	MRT (h)
A Mean	1.51	9.6	16.3	13.0	8.6	384.0	8.7
SD	0.98	4.6	4.2	5.5	4.0	88.4	3.5
B Mean	1.00	8.7	18.0	12.3	10.2	360.6	9.9
SD	0.64	1.2	5.2	2.7	1.8	91.8	1.6
Mean (overall)	1.26	9.17	17.2	12.6	9.35	372.9	9.3
SD	0.90	3.56	5.2	4.4	3.25	90.8	2.9

Cl, total body clearance; VDβ β-phase volume of distribution; Vd_{ss}, steady-state volume of distribution; MRT, mean residence time

In group A, samples were taken at the following times: before administration; 4, 6, 12, 24, 48, and 72 h after the commencement of administration; and at 10 and 30 min and 1, 2, 4, 6, 12, and 24 h after the end of the infusion. In group B, samples were taken on days 1–3 before, in the middle, and at the end of the infusion, and at 10 and 30 min and 1, 2, 4, 6, 12, 24, and 48 h after the end of the last infusion.

Drug analysis. Serum VP16 levels were determined by HPLC as described elsewhere [6]. Briefly, after the addition of teniposide as an internal standard, 1 ml serum was extracted by 5 ml chloroform. The organic phase was dried under vacuum and redissolved in 200 µl mobile phase. Then, an aliquot was injected into an HPLC system. Separation was achieved with an isocratic solvent system of methanol, acetic acid, 250 m*M* ammonium acetate buffer (pH 6.6) (54 : 1 : 45 by vol.), at a flow rate of 1.5 ml/min using a µBondapak C18 (10 µm) column. The detection was carried out electrochemically, with a potential of +900 mV; under the experimental conditions, the detection limit of VP16 was 20 ng/ml. The assay's percentage of coefficient variation on a day-to-day and a within-day basis was 7.1% and 3.9%, respectively. The reaction was linear between 50 ng/ml and 30 µg/ml.

Pharmacokinetic analysis. Serum VP16 concentration curves were fitted and pharmacokinetic parameters, estimated using the PHARM computer program [12]. The elimination half-life ($t_{1/2}$) was calculated from the equation $t_{1/2} = \ln 2/k$, where k is the elimination rate constant given by the slope of ln serum concentration vs time. The AUC was estimated by the trapezoidal method and extrapolated to infinity. The AUC obtained for the 3-day schedule after a total dose of 360 mg/m² VP16 was calculated by multiplying by 3 the AUC obtained after a single administration. The pharmacokinetic parameters obtained during the two modalities of administration were compared using Student's *t*-test.

Results

In all, 41 cycles of chemotherapy were given. All 19 patients were evaluable for toxicity but only 16 were evaluable for response.

Pharmacokinetics

VP16 pharmacokinetic parameters were determined during the first course of therapy in all patients. The mean concentration values vs time curves are shown for each group in Fig. 1. Whatever the schedule, plasma elimination showed a biexponential decay curve, with a mean distribution half-life of 1.26±0.9 h and a mean elimination half-life of 9.17±3.56 h. After a 72-h CVI, the steady-state plasma concentration of VP16 was obtained between 12 and 24 h after the beginning of the infusion and reached 5.0±0.32 mg/l. In the group receiving a fractionated daily dose, maximal plasma concentrations ranged from 15.1 to 26.9 mg/l (mean, 20.2±3.7 mg/l); no significant increase in VP16 levels at the 24-h mark was observed over the 3 consecutive days, indicating a lack of drug accumulation.

Table 1 shows the main pharmacokinetic parameters for all patients. For schedule A, the mean total body clearance (Cl) was 16.3±4.2 ml/min¹/m², and that for schedule B was 18.0±5.2 ml/min¹/m². No significant difference was noted. Moreover, the β-phase distribution volume (Vdβ) (13.0±5.5 l/m² for schedule A vs 12.3±2.7 l/m² for schedule B) showed no significant difference. Exposure of the patients to the drug as expressed by the AUC was also similar in the two groups.

Toxicity

Leukocyte, polymorphonuclear cell, and platelet count nadirs are summarized in Table 2. The nadir count medians of these three hematologic parameters were similar for the two schedules of administration. However, we noted that the number of courses yielding a WHO toxicity grade of >2 was higher for schedule B. In group A treatment was delayed for 1 week in three cases; in group B, a delay in treatment was necessary in two cases (1 and 2 weeks), a

Table 2. Comparison of hematologic toxicity of the two schedules of VP16 administration

		WBC nadir ($\times 10^9$/l)		Polymorphonuclear cell nadir ($\times 10^9$/l):		Platelet nadir $\times 100$ (10^9/l)	
	Cycles/patients (*n*)	Median (range)	Cycles with WHO grade >2/ patients (*n*)	Median (range)	Cycles with WHO grade >2/patients (*n*)	Median (range)	Cycles with WHO >2/patients (*n*)
Schedule A	17/7	3.6 (1.3–14.4)	2/1	2.0 (0.2–12.1)	4/2	200 (70–400)	0/0
Schedule B	25/9	4.0 (1.5–11.9)	3/3	1.8 (0.4–5.4)	4/4	210 (117–665)	0/0

decrease in dose (by 25%) was required in two patients. Gastrointestinal toxicity was similar for both protocols, and no neotoxicity due to CVI occurred.

Clinical response

All of the 16 patients evaluable for clinical response had pulmonary and/or hepatic disease. The responses were classified as complete response (CR), partial response (PR), no change (NC), and progressive disease (PD). Eight patients per group were evaluated. We noted only two PRs in group A and three in group B. Five patients (two in group A and three in group B) were classified as NCs.

Discussion

Our results confirm those previously reported by Bennett et al. [4]. From a pharmacokinetic point of view, VP16 shows good potential for CVI: steady-state concentration was obtained about 12–24 h after the start of the infusion. The concentration level achieved at the plateau is quite important; it reached 5.0 ± 0.32 mg/l ($n = 10$), corresponding to a total body clearance of 16.3 ± 4.2 ml/min^1/m^2. This clearance was lower than that reported by Bennett et al. [4] (24.5 ± 12.1 ml/min^1/m^2). This difference could be explained by the combination of VP16 and a prior administration of CDDP. Sinkule et al. [22] showed a significant decrease in VP16 systemic clearance in patients with prior cisplatin exposure, whereas Gouyette et al. [13] found no drug interaction. On the other hand, D'Incalci et al. [10] have suggested that the total body clearance of VP16 diminished in subjects with impaired kidney function and proposed that the dose must be reduced for such patients. However, all of our patients had normal serum creatinine levels as well as a calculated creatinine clearance of >60 ml/min^1/m^2.

No relationship was found between biological and pharmacokinetic parameters in the present study. However, Sinkule et al. [22] and Arbuck et al. [2] have described a correlation between transaminase or bilirubin levels and the systemic clearance of VP16. Relationships between pharmacokinetics and pharmacodynamics have been established by Bennett et al. [4] (correlation between the steady-state drug concentration and the leukocyte nadir) and by Brindley et al. [5] (relationship between the 24-h serum concentration and the WBC nadir in patients suffering from malignant teratoma, but no relationship in patients with choriocarcinoma). As previously reported by Sinkule et al. [22] in children, the lack of such a correlation was noticed in patients suffering from metastatic NSCLC.

How best to combine the administration of VP16 and CDDP in clinical practice remains unclear. Different schedules (i.v., p.o., CVI) have been used at different doses of the two drugs (60–80 mg/m^2 for CDDP and 80–120 mg/m^2 daily for VP16). These modifications have not enhanced the overall response rate, which ranges from 19% to 40% for NSCLC [3, 9, 15, 17–19, 24, 25]. Nevertheless, Slevin et al. [23] have reported that a multiple infusion of VP16 yielded a response rate significantly greater than that achieved with a single 24 h infusion. In terms of hematologic toxicity, the present study showed no difference between repeated infusions (3 days) and a 72-h infusion. These results disagree with those of Creagan et al. [8], who reported that hematologic toxicity was more severe when VP16 and CDDP were concomitantly infused over 120 h than when the two drugs were given by short infusion; however, their patients received lower doses of VP16 (20 mg/m^2 daily $\times 5$).

To date, only Matsushima et al. [20] have shown a time-schedule dependency for VP16: in a human tumor cell line derived from an adenocarcinoma of the lung, the degree of inhibition actived with 24-h drug exposure was >100-fold that observed with 1-h exposure. Other authors [11, 14] have speculated as to the mechanism of action of VP16, and their results suggest that its prolonged infusion may be more effective when it is combined with other drugs that directly damage DNA, as DNA breaks are rapidly repaired once VP16 is discontinued. These experimental data could probably explain the encouraging results obtained by Tschopp et al. [26], who combined amsacrine and CVI of VP16 in patients with relapsed and primarily resistant acute nonlymphocytic leukemia.

As the results of the present study showed no differences between the two modalities of VP16 administration in terms of clinical response, hematologic toxicity, or pharmacokinetics, we see no rationale in clinical practice for treating NSCLC patients with VP16 given as a CVI.

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