Phase I Clinical and Pharmacological Study of 72-Hour Continuous Infusion of Etoposide in Patients with Advanced Cancer

Charles L. Bennett, Joseph A. Sinkule, Richard L. Schilsky, Elizabeth Senekjian, and Kyung E. Choi

ABSTRACT

Etoposide (VP-16) is a semisynthetic epipodophyllotoxin that exhibits cell cycle phase specific cytotoxicity and enhanced effectiveness with increasing duration of drug exposure. We have therefore conducted a Phase I trial to determine the side effects, tolerable doses, and pharmacokinetic parameters of VP-16 given by continuous i.v. infusion to patients with advanced cancer. Eighteen patients were treated with varying dosages of VP-16 infused continuously for 72 consecutive hours every 28 days. Using this schedule, the maximally tolerated dosage of VP-16 was 150 mg/m²/day for patients with good performance status and 125 mg/m²/day for more debilitated cancer patients. Hematological toxicity was dose limiting with median granulocyte and platelet nadirs of 700/mm³ and 116,000/mm³, respectively, at a dose of 150 mg/m²/day. Other toxicities included only mild nausea, vomiting, and alopecia. Plasma and urine VP-16 concentrations were determined using a high-performance liquid chromatography assay. At a VP-16 dosage of 150 mg/m²/day, steady-state VP-16 concentrations were in the range of 2.1 to 7.0 μg/ml in all patients. Further pharmacokinetic analysis revealed that the plasma clearance of VP-16 was consistently near 25 ml/min/m² (independent of dosage) and that renal clearance accounted for only 15% of VP-16 total plasma clearance. Patient age was found to be the most important factor correlating with plasma clearance of VP-16. Linear regression analysis also revealed that both the plasma VP-16 concentration at steady state and the concentration of VP-16 in plasma at 24 h from the start of the infusion correlated with hematological toxicity; no other patient characteristics correlated with hematological toxicity. The recommended VP-16 dose for Phase II trials of 72-h continuous infusion VP-16 is 150 mg/m²/day in patients with good performance status.

INTRODUCTION

VP-16 is an anticancer agent with proven efficacy in several human malignancies (1–2). Although the mechanism of action of the drug is not completely understood, it appears to exert its cytotoxic effects by inhibition of the enzyme topoisomerase II, resulting in DNA strand scission (3). Etoposide also delays cell transit through S phase and produces cell cycle arrest in the late S or early G2 phase; it is most effective when cells are in S or G2 phase (1, 4). This cycle-dependent cytotoxicity of VP-16 probably explains the greater antitumor activity of VP-16 when administered as frequent, rather than as single doses in mice or G2 phase (1, 4). This cycle-dependent cytotoxicity of VP-16 probably explains the greater antitumor activity of VP-16 when administered as frequent, rather than as single doses in mice.

MATERIALS AND METHODS

Patient Selection

Patient demographic characteristics are shown in Table 1. Eighteen patients, 9 men and 9 women, ranging from 24 to 71 years of age, were entered in the study. All patients had a pathologically confirmed diagnosis of cancer and, in each case, the disease had proven refractory to standard therapy or was one for which no therapy of proven benefit was available. All patients had been previously treated with chemotherapy and/or radiation therapy. Each patient had an initial complete medical history and physical examination, complete blood and platelet count, and determination of serum chemistries. Complete blood and platelet counts were then obtained weekly during therapy, while all other parameters were repeated on Day 1 of each cycle. Prior to beginning chemotherapy, all patients had adequate renal and liver function, i.e., serum creatinine ≤2.5 mg/100 ml, and total bilirubin ≤3.0 mg/100 ml. A WBC ≥3500 cells/mm³, platelet count ≥100,000/mm³, and hemoglobin ≥10 g/dl were required prior to study entry.

Treatment Plan

Etoposide was given as a continuous i.v. infusion for 72 consecutive hours. The initial dose of 75 mg/m²/day was chosen based on the data available from the 120-h continuous infusion study of Aisner et al. (9), and extrapolation of the previously reported teniposide data and dosage scheme (8). One-half of the daily dose of VP-16 was mixed in 500 ml of 5% dextrose in water-0.45% normal saline and infused over 12 h. Dose escalation was carried out according to the following scheme. Level I, 75 mg/m²/day; Level II, 100 mg/m²/day; each subsequent level had an incremental VP-16 dosage increase of 50 mg/m²/day. Three patients were entered at each dose level and evaluated prior to dosage escalation in subsequent patients. In addition, individual patients were escalated to the next highest level if severe toxicity (WBC nadir <2000/...
CONTINUOUS INFUSION OF VP-16 IN ADVANCED CANCER PATIENTS

mm³ or platelet count nadir <50,000/mm³ did not occur. Cycles of chemotherapy were repeated every 28 days. Patients were treated for at least two cycles of therapy unless rapid disease progression or unacceptable toxicity occurred.

Pharmacokinetic Studies

Sample Collection. Plasma and urine VP-16 concentrations were determined in several patients at each dosage level studied. Ten ml of heparinized blood were obtained prior to the start of chemotherapy, twice daily over the VP-16 infusion, and at 3, 6, 12, and 24 h following the end of the infusion. Blood was immediately centrifuged and the plasma was decanted and frozen at -70°C until the time of analysis. During chemotherapy administration, all urine was quantitatively collected in 24-h aliquots for determination of VP-16 concentrations and renal clearance. Samples were refrigerated during collection and, at the completion of each 24-h period, the total volume was accurately measured and aliquots were frozen at -70°C.

Drug Analysis. Etoposide concentrations were determined using a sensitive and specific high-performance liquid chromatography assay (11). Briefly, a reverse-phase 10-μm phenyl column was eluted with an isocratic mobile phase of water:acetonitrile:glacial acetic acid (74:25:1) at a flow rate of 1.0 ml/min. A model 481 variable wavelength detector (Waters Associates, Milford, MA) and a model 510 pump (Waters Associates) were used. Detector output at 254 nm was processed by a Hewlett Packard HP 3390A data integrator.

Sample Preparation

Plasma samples were extracted with ethyl acetate after addition of 0.5 ml (NH₄)₂SO₄ and the internal standard (VM-26, teniposide). Urine samples were centrifuged to remove sediment, diluted 1:4 with distilled water, and 50 μl were injected directly onto the high-performance liquid chromatography column. The peak height ratio of VP-16 to internal standard for plasma was plotted against known concentrations of VP-16 (1.0–10.0 μg/ml), and this linear calibration curve was used to determine drug concentrations in patient samples. Urine samples were determined against a standard calibration curve of 0.1–5 μg/ml with a daily variation of less than 10%.

Clearance Determinations

VP-16 plasma clearance at steady state was determined by using the formula:

\[ CL_p(\text{ml/min/m²}) = \frac{\text{Infusion rate (mg/m²/min)}}{C_{\text{p,mean}}(\text{μg/ml})} \]

Creatinine clearance (CLcr) was estimated using the formula:

\[ CL_{cr}(\text{ml/min/m²}) = \frac{(140 - \text{patient's age}) \times \text{weight (kg)} \times 0.85 (\text{if female})}{P_{cr} (\text{mg} / 100 \text{ml}) \times (1440 \text{ min}) \times \text{body surface area (m²)}} \]

(\( P_{cr} = \text{plasma creatine concentration} \))

The renal clearance of VP-16 (\( CL_r \)) was determined using the formula:

\[ CL_r(\text{ml/min/m²}) = \frac{\text{Urine concentration (mg/ml)} \times \text{urine volume (ml/min/m²)}}{C_{\text{um}}(\text{mg/ml})} \]

\( C_{\text{um}} \) was defined as the mean of the measured plasma concentrations of VP-16 obtained at 24, 36, 48, and 72 h after the initiation of the infusion.

Statistical Analysis

Statistical analysis of the data was performed using the RS/1 software package (Bolt, Beranek and Newman, Inc., Cambridge, MA) on a Digital Professional 350 microcomputer. The effect of clinical parameters on the pharmacokinetics of continuous i.v. infusion of VP-16 was evaluated by using univariate and stepwise multiple regression analysis. Student's 2-way t test was used to test for differences in subgroups of data.

RESULTS

Clinical Study. Eighteen patients received a total of 36 cycles of chemotherapy with continuous infusion VP-16 during this study. One patient died of bacterial sepsis 10 days after completing his chemotherapy treatment; all other patients received at least one full cycle of therapy and were followed for at least 1 month.

The major clinical toxic effect observed during this study was bone marrow suppression. As shown in Table 2, escalation of the VP-16 dose was associated with increasing neutropenia and thrombocytopenia. Significant neutropenia (absolute neutrophil count <1000 cells/mm³) and thrombocytopenia (platelets <100,000/mm³) were noted in the first 2 patients treated with 150 mg/m²/day of VP-16; therefore, all subsequent patients were started at a VP-16 dose of 125 mg/m²/day and escalated to 150 mg/m²/day if severe toxicity was not observed. Patients

<table>
<thead>
<tr>
<th>VP-16 dose (mg/m²/day)</th>
<th>No. of patients/no. of cycles</th>
<th>Hematological median nadir (range) x 1000/mm³</th>
<th>Gastrointestinal (nausea/vomiting)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WBC</td>
<td>PMN</td>
</tr>
<tr>
<td>75</td>
<td>3/3</td>
<td>5.5</td>
<td>4.1</td>
</tr>
<tr>
<td>100</td>
<td>8/9</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
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<td>12/14</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>150</td>
<td>7/9</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>200</td>
<td>1/1</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

* Grade I or II only.
* PMN, polymorphonuclear cells.
who were scheduled to have dose escalation from 100 mg/m²/day of VP-16 to 150 mg/m²/day were escalated instead to 125 mg/m²/day of VP-16 on their next cycle. Significant neutropenia and/or thrombocytopenia were noted in 5 of 7 patients treated with 150 mg/m²/day of VP-16. All but one of these patients had a performance status of 1. Six of 12 patients had significant hematological toxicity when treated with 125 mg/m²/day of continuous i.v. infusion of VP-16. These 6 patients tended to be somewhat more debilitated prior to study entry (CALGB performance status of 1 in only one patient and CALGB performance status of 2 in the other 5 patients). Fifty to 60% of all patient cycles at dosages of 125 to 150 mg/m²/day of etoposide were associated with a WBC nadir less than 3000 cells/mm³, absolute neutrophil count nadir less than 1000 cells/mm³, and/or a platelet count nadir of less than 100,000/mm³. Thus, we conclude that the maximally tolerated VP-16 dose was 150 mg/m²/day in good performance status patients. Complete hematological recovery occurred by Day 28 in virtually all patients; however one patient with renal cell carcinoma died with neutropenic sepsis (nadir absolute neutrophil count of 300 cells/mm³) 10 days after his first treatment with continuous infusion VP-16 (125 mg/m²/day). Autopsy revealed infarcted colon and extensive hepatic metastases. Stepwise multiple regression analysis of nadir WBC versus VP-16 dose, age, sex, and prior treatment with cisplatin was performed. Age was significantly correlated with nadir WBC (r = -0.72; P = 0.01); no other significant relationships were noted.

Other notable side effects included alopecia in virtually all patients, and mild nausea and vomiting. In general, the chemotherapy was well tolerated with CALGB Grade I or II nausea and vomiting being noted in 42% of the cycles (see Table 2). No patient experienced Grade III nausea or vomiting. In addition, no cardiovascular toxicities or mucositis were noted. Alterations in renal or hepatic function were not noted in this Phase I trial.

Although the primary objective of this study was to determine the toxicities, maximally tolerated dose, and pharmacokinetics of 72-h continuous infusion of VP-16, patients with clearly measurable lesions were evaluated for response to treatment using standard response criteria. No complete or partial responses occurred. One patient with a mediastinal non-seminomatous germ cell tumor had stable disease during 4 cycles of therapy. He was then lost to further follow-up without evidence of disease progression.

Pharmacokinetic and Pharmacodynamic Studies. Etoposide pharmacokinetics was determined during 17 cycles of chemotherapy in 10 patients. Since dose escalations were permitted in individual patients, some patients were studied at more than one dose level. Table 3 displays the steady-state plasma concentrations of VP-16 achieved at varying doses. Considerable intrapatient variability was noted; indeed, at the maximally tolerated dose of 150 mg/m²/day, plasma VP-16 concentrations ranged from 2.1 to 7.0 μg/ml.

Table 3 Pharmacokinetic parameters of continuous infusion VP-16

<table>
<thead>
<tr>
<th>VP-16 dose (mg/m²/day)</th>
<th>No. of patients/cycles</th>
<th>Cmax (μg/ml)</th>
<th>Clp (ml/min/m²)</th>
<th>CL (ml/min/m²)</th>
<th>% of CL/Clp</th>
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<tr>
<td>75</td>
<td>2/2</td>
<td>2.3 ± 1.6a</td>
<td>230 ± 1.6</td>
<td>6.0</td>
<td>20.2</td>
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<tr>
<td>100</td>
<td>6/7</td>
<td>3.2 ± 1.1</td>
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<tr>
<td>125</td>
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<td>30.1 ± 22.7</td>
<td>2.50 ± 1.0</td>
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</tr>
<tr>
<td>150</td>
<td>3/5</td>
<td>4.7 ± 1.5</td>
<td>27.7 ± 11.6</td>
<td>2.27 ± 1.2</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>200</td>
<td>1/1</td>
<td>5.2</td>
<td>26.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Mean ± SD.

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Examination of concentration versus time plots for individual patients (not shown) revealed little intrapatient variability during the 72-h infusion. While there was a tendency for the plasma etoposide concentration to increase slightly over time, etoposide concentrations at the completion of the 72-h infusion were not significantly higher than those determined 24 h into the infusion (P > 0.05, log rank test). Since etoposide doses were routinely escalated to toxicity, few patients had pharmacokinetic data obtained during multiple cycles of therapy at the same dose level. Thus, intrapatient variability over multiple courses of treatment cannot be reliably assessed.

Data on plasma and renal clearance of etoposide are also shown in Table 3. Mean plasma clearance of VP-16 was consistently near 25 ml/min/m². Renal clearance (Clr) averaged 3.4 ± 2.4 (SD) ml/min/m² (range from 1.1 to 12.2 ml/min/m²) and accounted for approximately 15% of VP-16 plasma clearance.

Pharmacodynamic and pharmacokinetic relationships were examined using regression analysis. Stepwise multiple regression analysis of dose, Clp, age, sex, prior cisplatin, and serum albumin, versus Clp was performed. Plasma VP-16 clearance correlated best with age (r = -0.75; P = 0.01), i.e., clearance tended to decline with increasing age. No other significant relationships were noted.

Since the major drug-related toxicity was bone marrow suppression, we attempted to identify a pharmacokinetic parameter that might be predictive of hematological toxicity. The mean Cmax in patients with significant hematological toxicity (granulocyte nadir <1000 cells/mm³ and/or platelet nadir <100,000/mm³) was 4.7 ± 2.2 μg/ml; while patients without this degree of hematological toxicity had a significantly lower mean steady-state plasma etoposide concentration of 2.7 ± 1.2 μg/ml (P < 0.05).

To attempt to minimize the impact of intrapatient variability in pretreatment WBC, we also examined the relationship between surviving fraction of the WBC and VP-16 plasma concentration. This approach has been used in evaluating the pharmacodynamics of other anticancer drugs (12, 13) and uses the following formulas:

SF = \frac{\text{Nadir WBC}}{\text{Pretreatment WBC}} \quad (A)

SF = A e^{-ktC_{mu}} \quad (B)

where \( t \) is time; \( A \) and \( k \) are constants and \( C_{mu} \) is concentration of drug in plasma at steady-state.

From Eq. B:

\ln SF = \ln A - ktC_{mu} \quad (C)

From Eq. C:

\ln SF = A' - k' C_{mu} \quad (D)

where \( k' \) is \( kt \) and \( A' \) is \( \ln A \).

For each of the 10 patients in whom pharmacological data were obtained, \( C_{mu} \) was determined from the most complete data set (usually the first treatment cycle) and correlated with the ln SF for that treatment cycle. Using Equation D, linear regression analysis of \( C_{mu} \) versus ln SF demonstrated a highly significant relationship (r = -0.89; P = 0.001) (Fig. 1). No other patient characteristics (dose, age, sex, and prior cisplatin therapy) had a significant correlation with ln SF.

Concentration versus time plots generated for individual patients (not shown) revealed that steady-state concentrations of VP-16 were reached between 15 and 24 h after initiation of
therapy. A significant correlation between \( C_{\text{ps}} \) and the plasma concentration of VP-16 at 24 h after therapy initiation (\( C_{24h} \)) was noted (\( r = 0.94; P < 0.05 \)). Linear regression analysis revealed that \( C_{24h} \) also correlated with ln SF (ln SF = 0.19–0.26 \( C_{24h}; r = -0.89; P = 0.001 \)).

**DISCUSSION**

The results of this Phase I study of continuous infusion VP-16 indicate that the drug may be given by continuous infusion for 3 days with tolerable toxicity. The dose-limiting toxicity was myelosuppression, manifest as both neutropenia and thrombocytopenia. Other toxicities included nausea, vomiting, and alopecia. The maximally tolerated dosage was 150 mg/m\(^2\)/day (450 mg/m\(^2\)/course) for patients with good performance status and 125 mg/m\(^2\)/day (375 mg/m\(^2\)/course) for more debilitated patients.

Aisner et al. (9) suggested a similar maximally tolerated dosage in their study of 120-h continuous infusion of VP-16 in cancer patients with similar demographic characteristics; they also noted primarily hematological and gastrointestinal toxicities. In addition, two patients had anteroseptal myocardial infarctions and one patient developed fatal congestive heart failure. In an earlier Phase I study of continuous infusion VP-16, Lokich and Corkery (10) also noted occasional episodes of significant congestive heart failure. The reduced saline load used in the present study may partially account for the absence of episodes of fluid overload in our patients.

All pharmacokinetic studies of VP-16 to date have been carried out with the drug given as short infusions administered daily or infusions lasting 24 h. In each of these studies parent drug concentrations were measured by use of radioisotopic techniques (14) or, more recently, by high-performance liquid chromatography methods (15, 16). A summary of the pharmacokinetic parameters determined in this study and, for comparative purposes, the values previously reported for patients given short infusions on a daily schedule are shown in Table 4. Our data are also in agreement with pharmacokinetic data obtained by D’Incalci et al. (17) in a study of three patients given 72-h continuous infusion VP-16 (100 mg/m\(^2\)/day). Indeed, the mean values derived in our study did not differ significantly from the average pharmacokinetic parameters reported previously except that the mean renal clearance of etoposide (3.3 ± 2.3 ml/min/m\(^2\)) and the proportion of drug eliminated in the urine (15 ± 9%) are somewhat lower than that reported in other studies using short (30–60 min) infusion (14, 18–20) (see Table 4).

As a group, our patients tended to have moderately impaired renal function which may account for the lower renal clearance of etoposide observed. Patients were eligible for entry to the study with plasma creatinine as high as 2.5 mg/100 ml and the mean creatinine clearance for the entire group was only 37.2 ml/min/m\(^2\). In contrast, most previously reported studies of etoposide pharmacokinetics limited eligibility to patients with normal renal function defined as plasma creatinine ≤1.2 mg/100 ml and creatinine clearance ≥60 ml/min. Recently, D’Incalci et al. (21) reported that patients with severely impaired renal function (mean creatinine clearance 26.1 ml/min) had markedly reduced plasma clearance and urinary excretion of etoposide compared to patients with normal renal function. These investigators also noted a significant correlation between plasma etoposide clearance and renal creatinine clearance in patients with a broad range of creatinine clearances (4 ml/min to greater than 100 ml/min). Our data do not permit a similar analysis due largely to the much narrower range of creatinine clearance values in our patients. All but one of our patients had a creatinine clearance greater than 45 ml/min but no patient had a creatinine clearance greater than 95 ml/min. Thus, we have been unable to detect a significant correlation between plasma drug clearance and renal function. Interestingly, inspection of the data of D’Incalci et al. suggests a much poorer correlation of plasma etoposide and renal creatinine clearance in those patients with only moderately impaired or normal renal function.

There are known physiological changes that occur in elderly patients that may affect drug disposition. For example, reduced renal function and delayed methotrexate clearance may explain the increased incidence of severe hematological toxicity associated with the use of this drug in patients over 70 years old (22). Many protocols exclude patients older than 70 or impose mandatory dosage reduction for patients in the 60- to 70-year age range. Empiric dose reduction of cyclophosphamide, methotrexate, and 5-fluorouracil based on creatinine clearance has been used in the treatment of elderly women with breast cancer in an effort to minimize age-related toxicity (23). There is evidence however that properly administered high-dose induction chemotherapy for acute leukemia is equally well tolerated by both elderly and young patients (24), and a recent review of elderly patients enrolled on Eastern Cooperative Oncology Group protocols revealed that many chemotherapeutic agents do not cause more severe toxicity in these individuals (22). No study has specifically examined the pharmacokinetic profile of any anticancer drug in relationship to patient age.

In our study, statistical analysis revealed that age was the most important factor correlating with plasma clearance of VP-16 (older patients had lower clearance of VP-16). In addition, age significantly correlated with severity of hematological toxicity, as assessed by nadir WBC. Therefore, elderly patients...
may need to be monitored more closely for hematological toxicity when receiving continuous infusion VP-16.

The dose-limiting toxicity in this study was myelosuppression, specifically, neutropenia and thrombocytopenia. Our analysis demonstrated that patients with severe myelosuppression (WBC <1000 cells/mm$^3$ and/or platelets <100,000 cells/mm$^3$) had significantly higher steady-state VP-16 plasma concentrations compared to those with less severe toxicity. In addition, we have demonstrated a significant relationship between the surviving fraction of the WBC and the steady-state and 24-h plasma VP-16 concentrations. This suggests that pharmacokinetic monitoring with determination of the 24-h VP-16 concentration may be useful in prospectively identifying those patients at risk of developing severe hematological toxicity while receiving continuous infusion VP-16.

VP-16 has been shown to have antineoplastic activity against several human tumors. Its mechanism of antitumor action has not been precisely determined, although it causes metaphase arrest and produces single-stranded DNA breaks (25). In vitro data using L1210 cells suggest that increasing the duration of VP-16 exposure may improve response (5). In clinical studies in patients with small cell lung cancer, schedule dependency has been shown with a significant increase in the response rate in patients receiving etoposide for 5 consecutive daily treatments as compared to administration of the same dose once every 21 days (26). Studies with continuous i.v. infusion of VP-16 given in combination with other chemotherapeutic agents have also shown encouraging results. Tschopp et al. (27) reported a 47% complete remission rate with 4'-9-acridinylamino)methanesulfon-m-anisidine plus continuous infusion VP-16 in 38 patients with refractory acute nonlymphocytic leukemia. An earlier study with these same two drugs reported only a 20% complete remission rate in similar patients with refractory acute nonlymphocytic leukemia when both drugs were given by bolus administration (28). DNA breaks are apparently more sensitive to VP-16 than the mandrel root from Iaryk-Kul. Am. J. Med., 72: 136–144, 1982.


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