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# Pharmacokinetics of oral etoposide in patients with hepatocellular carcinoma

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**Abstract** Etoposide dosage in patients with liver dysfunction remains controversial. Since etoposide has a hepatic component to its clearance (CL) and shows a high degree of protein binding, hepatic impairment could affect etoposide disposition. However, the empiric recommendation that the dose of etoposide be decreased in such patients may reduce systemic exposure and be detrimental to its antitumor activity. To address these issues we studied the pharmacokinetics (PK) of etoposide in patients with hepatocellular carcinoma (HCC) and underlying cirrhosis ($n = 17$) treated with daily oral etoposide. Unbound etoposide was obtained by ultrafiltration. Etoposide concentrations (total and free drug) were measured by high-performance liquid chromatography (HPLC) and analyzed by noncompartmental equations. The patients had mild or moderate liver dysfunction. Albuminemia was in the normal range for all the patients. Creatininemia was normal in all but two patients. PK results (mean and range) showed that etoposide disposition was unchanged in patients with liver dysfunction. We found slightly high etoposide bioavailability [F, 61% (17–95%)] and clearance [CL, 1.1 (0.7–2.3) l $h^{-1}$ $m^{-2}$] resulting in a normal degree of systemic exposure ($AUC_{oral}$ 27 μg h $ml^{-1}$). Normal protein binding [PB 93.2% (84.4–98.1%)] contributed to a normal level of exposure to free drug ($AUC_{f,\ oral}$ 1.9 μg h $ml^{-1}$). The distribution volume [$V_{SS}$ 8.4 (6.1–13.2) l/$m^2$] and the effective half-life [$t_{1/2eff}$, 5.1 (3.0–9.6) h] were normal. Median CL and protein binding did not differ in the seven patients with total bilirubin value of $> 1.2$ mg/dl as compared with the ten patients with total bilirubin levels of $\leq 1.2$ mg/dl (1.3 versus 1.0 l $h^{-1}$ $m^{-2}$ and 92.5% versus 93.4%, respectively). In agreement with this PK finding, we observed no clinical evidence of increased toxicity in patients with hyperbilirubinemia as compared with patients with normal bilirubinemia (mean WBC decrease 38% versus 47%). The only case of severe (grade 4) hematological toxicity was observed in one patient with reduced glomerular filtration. Since the pharmacological effects of etoposide correlate with the level of systemic exposure to the free drug, our data suggest that no dose reduction is needed in patients with HCC. It is even possible to increase the dose intensity in patients with favorable PK parameters under appropriate hematological and therapeutic drug monitoring.

**Key words** Etoposide · Pharmacokinetics (PK) · Protein binding · Liver dysfunction

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## Introduction

The controversy over etoposide dosage in patients with liver dysfunction has not yet been solved. Since etoposide is partially cleared by the liver and shows a high degree of protein binding, hepatic impairment could reduce etoposide disposition by lowering intrinsic hepatic CL and increase the free drug concentration ($C_f$) by lowering binding to plasma proteins. This would result in higher levels of systemic exposure to the pharmacologically active free drug and, therefore, lead to greater toxicity. The knowledge of etoposide pharma-

cokinetic (PK) behavior in clinical situations normally believed at "high risk" for toxicity could help in the treatment of patients with the theoretically active dose of the drug by reducing this drawback. Ideally, the dose should be adjusted after therapeutic drug monitoring (TDM). New studies focusing on evaluation of the "therapeutic level" of the drug are needed to establish the role of TDM in standard practice. Of course, the PK parameters should be carefully compared with the clinical characteristics of the patients, mainly the performance status (PS), organ functioning reserve, and pretreatment.

Etoposide is a semisynthetic epipodophyllotoxin derivative widely used to treat a variety of solid tumors and hematological malignancies [9]. Myelosuppression is dose-related and is the dose-limiting toxicity. Etoposide has a mixed clearance (CL, renal and hepatic; 20 ml $min^{-1}$ $m^{-2}$) and a high degree of protein binding (about 95%). Although etoposide is largely renally excreted (50%), there is a significant nonrenal component to its elimination. Approximately 20–40% of the extrarenal CL occurs by glucuronide formation in the liver [11]. About 1–16% of parent drug and metabolite elimination occurs through biliary excretion [3]. For an extensively protein-bound drug, even minimal changes in protein binding cause important changes in the free fraction of drug. Since only unbound drug is available for membrane transport and receptor interaction, the $C_f$ is a major determinant of the pharmacological effect. Impairment of hepatic function and/or alterations in plasma protein binding could alter the disposition (and, possibly, the pharmacological effect) of etoposide. Liver disease could potentially decrease the rate of etoposide metabolism (intrinsic hepatic CL) and biliary excretion. Hyperbilirubinemia could increase the fraction of unbound etoposide by its displacement from plasma proteins and hypoalbuminemia could also contribute to enhancement of the $C_f$ [19]. All these factors may be responsible for an enhanced systemic exposure to total and free etoposide.

Since the parent drug has antineoplastic activity (whereas most metabolites do not) [7], impaired PK could increase the pharmacodynamic (PD) effects. Liver function tests are frequently used to adjust doses of drugs cleared by the liver. However, many processes are involved in hepatic CL, and these do not correlate highly with biochemical measures such as bilirubin. Thus, the empiric recommendation that the dose of etoposide be decreased by 50% (total bilirubin 1.5–3.0 mg/dl) or even omitted (total bilirubin $>5.0$ mg/dl) in patients with abnormal bilirubin levels [14] to avoid severe hematological toxicity may reduce systemic exposure and be detrimental to the drug's antitumor activity. Conclusive PK and toxicity data to justify these recommendations are not yet available. Several PK studies have been done in recent years in cancer patients with renal or hepatic insufficiency [1, 5, 10, 11, 20]. Most authors agree that etoposide doses should be reduced in patients with renal impairment because plasmatic CL of etoposide shows a positive linear correlation with creatinine CL [1, 5]. On the other hand, etoposide dosage in patients with liver dysfunction is not definite [5, 20]; some investigators suggest that etoposide doses be reduced [20], but others indicate that no dose reduction is needed [1, 5, 11]. Thus, rational dosing guidelines have not been clearly defined for etoposide in cases of liver failure.

Chronic oral low-dose etoposide has shown promising results in some tumors [4]. An increase in its efficacy because of prolonged inhibition of topoisomerase II associated with good safety makes it particularly attractive. Since oral etoposide has shown some activity in hepatocellular carcinoma (HCC) [2] and no standard therapy is currently available for this malignancy, in our institution it has been used to treat patients with advanced HCC. In an attempt to evaluate whether these patients could safely be given full doses of etoposide or, alternatively, whether they would require a dose adjustment because of liver impairment, we performed a clinical PK study of chronic oral etoposide in this group of patients with advanced HCC and underlying cirrhosis.

## Patients and methods

### Patients and eligibility criteria

Patients with histologically documented multifocal unresectable or metastatic HCC were enrolled in this study. They had to be in progression after transcatheter intraarterial chemoembolization (TACE), but patients not eligible for TACE were also accepted. An age of more than 18 years, an expected survival of 3 months, a performance status of at least 60 (Karnofsky), a minimal WBC count of 4 000/μl, and a minimal platelet count of 100 000/μl were required. The study was approved by the institutional review board. Informed consent was obtained in accordance with institutional guidelines. These patients had various degrees of liver dysfunction due to the neoplastic disease itself and/or to other concomitant diseases (underlying cirrhosis and hepatitis of alcoholic or viral etiology) and/or to previous hepatotoxic treatments (TACE). Standard laboratory tests were performed in all patients before the beginning of etoposide treatment. Concurrent long-term therapies were continued during the pharmacological monitoring.

### Liver assessment

Several liver function tests were performed within the 48-h period before the PK study. These included standard liver function tests such as determinations of serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), γ-glutamyltransferase (γ-GT), albumin, total bilirubin, and the prothrombin time index (PT index) and a quantitative liver function test (MEGX). The latter was performed as follows: two blood samples were drawn, one just before (blank or drug-free) and the other at 30 min after the bolus intravenous injection of a 1-mg/kg dose of lidocaine. Lidocaine is metabolized into a compound called monoethylglicynexylidide (MEGX) by the liver cytochrome P450 enzymatic system. The circulating level of MEGX (in micrograms per liter) was measured by a fluorescence polarization immunoassay (FPIA; Abbott TDX, Abbott Diagnostic Ltd, Rome, Italy) whose limit of quantitation is 10 μg/l. Quality-control samples containing 50, 100, and 200 μg/l were run during analyses, and the interday variability was within 10% (95% confidence interval). Pugh's modification of Child's grading (Child-Pugh score) [13] was the system used to assess the overall functional severity of liver disease. This system is based on the measurement of clinical and biochemical

parameters such as encephalopathy, ascites, bilirubin, albumin, and prothrombin; the greater the abnormality of such parameters, the higher the score. Patients whose score totals 5 or 6 are considered to be grade A; those scoring 7–9, grade B; and those with a score of 10–15, grade C. Patients were divided into two groups according to bilirubinemia: group 1 comprised patients within the normal range ($\leq$ 1.2 mg/dl), and group 2 consisted of patients with bilirubin values above the normal range ($>$ 1.2 mg/dl).

### Drug formulation and administration

The drug was given orally in the form of soft gelatin capsules. Etoposide capsules for clinical use (Vepesid) were obtained from Bristol-Myers Squibb (Latina, Italy). They contained 100 mg etoposide dissolved in a hydrophilic solution of citric acid, glycerol, water, polyethylene glycol 400, gelatin, parabens, and titanium oxide and iron oxide pigment. Each patient received a daily fixed oral dose of etoposide (100 mg) over 14 days; this schedule was repeated every 3 weeks until progression of disease or severe toxicity. An attempt was made to deliver at least two courses of chemotherapy before the response evaluation, even though five patients had to suspend etoposide therapy after only one cycle because of early progressive disease (three patients) and death (two patients).

### Bioavailability study and sample collection

The PK study was performed during the first cycle of chemotherapy on days 1 and 8 (after a 48-h washout period), when an oral dose (100 mg) and an intravenous dose (50 mg) were given in a randomized order to exclude an order effect. The intravenous dose was half the oral one because etoposide bioavailability is reported to be about 50% [17]. The parenteral formulation was given as a peripheral intravenous infusion (1 h) in 250 ml 0.9% saline solution. Each subsequent course lasted 3 weeks; daily 100-mg oral doses of etoposide were given for 14 consecutive days, followed by 7 days off chemotherapy. The first course was modified slightly because of the bioavailability study: 13 doses instead of 14 were given (no dose on the 7th day), and 1 of them (on the 1st or 8th day) was given intravenously (50 mg) instead of orally. Blood samples were drawn at 1, 2, 4, 6 and 24 h after etoposide administration via both the oral and the intravenous route (in the second case blood sampling was done at the aforementioned times after the onset of drug infusion). In both cases a blank blood sample was taken shortly before drug administration. All blood samples were collected in heparinized tubes and were immediately centrifuged to remove red cells; the obtained plasma samples were stored at −20 °C until assayed.

### Determination of protein binding

The protein binding was determined at peak ($C_{max}$) from total and free etoposide concentration data as:

$$\%PB = [1-(C_{max,f}/C_{max,t})] \times 100.$$

The unbound drug in each plasma sample analyzed for total drug was measured after ultrafiltration on Amicon Centrifree filters (Beverly, Mass. USA) whose membrane molecular-weight cutoff was 30 000.

### Total and unbound etoposide plasma concentration assay

Plasma concentrations were analyzed by reversed-phase high-performance liquid chromatography (HPLC) methods with UV (total etoposide) and fluorimetric (free etoposide) detection (they have been described elsewhere in more detail) [15].

#### *Total drug concentration*

$C_t$ was determined by the technique described by Evans et al. [8] and modified by D'Incalci et al. [5]. The chromatography apparatus consisted of a Waters 510 pump, a Waters 717 autoinjector equipped with a 200-µl loop, a Waters 3.9 × 300-mm µBondapak phenyl column, and a Waters 481 LC spectrophotometer coupled to Millennium 2010 chromatography manager software (Waters Associates, Milford, Mass., USA). The UV spectrophotometer was set at 254 nm. The mobile phase (a mixture of acetonitrile-water-glacial acetic acid, 35:61:1, by vol.) was eluted at 1.0 ml/min. Teniposide was used as the internal standard (IS), and samples were extracted using a liquid-liquid extraction process. In brief, each 1-ml plasma sample was spiked with teniposide (10.0 µg) and 8 ml of chloroform was added. After agitation (20 min) and centrifugation (1,000 *g* for 5 min), the upper aqueous layer was discarded by aspiration and the organic extract was evaporated to dryness by heating (40 °C) under vacuum. The dry residue was reconstituted in methanol (100 µl), and 25 µl of this solution was used for HPLC analysis. Quantitation was based on the IS method using the ratio of peak areas of etoposide and teniposide (IS) and a calibration curve for concentrations ranging between 0.2 and 10.0 µg/ml, with the limit of sensitivity being 0.2 µg/ml. The calibration curve was obtained from five plasma samples (1 ml) spiked with known amounts of etoposide (0.2, 0.5, 1.0, 5.0, and 10.0 µg/ml) and teniposide (10.0 µg/ml).

#### *Free concentration*

$C_f$ was determined by a technique validated in our laboratory [15]. The chromatography apparatus and conditions were similar to those described for the total drug except for only a few differences. Instead of UV absorbance detection, fluorimetric detection was used to increase sensitivity; consequently, the LC spectrophotometer was replaced by a Waters 470 fluorescence detector using 288 and 328 nm as excitation and emission wavelengths, respectively. A 60-min washout period was necessary between two sample runs to allow the elution of late fluorescing compounds, which can interfere with subsequent analyses. In brief, each 1-ml plasma sample was ultrafiltered using the disposable Centrifree Micropartition device from Amicon (Beverly, Mass., USA) for the separation of free etoposide. After centrifugation (2,000 *g* for 30 min at 25 °C), about 500 µl of ultrafiltrate was obtained from the starting plasma sample. The 500-µl ultrafiltrate sample was spiked with the IS teniposide (0.5 µg) and 1 ml of chloroform was added. After agitation (20 min), centrifugation (1,000 *g* for 5 min), and removal of the aqueous phase the organic extract was dried and rediluted in methanol (50 µl); 25 µl of this solution was injected. The calibration curve was constructed using five ultrafiltrate samples (500 µl) spiked with 0.5 µg of teniposide and 0.025, 0.050, 0.100, 0.250, and 0.500 µg of etoposide. The limit of quantitation was 0.050 µg/ml. In this range of concentrations, intraday and interday variabilities were within 15%.

### Pharmacokinetic analysis

A noncompartmental method was used to determine each patient's etoposide PK. The area under the concentration-time curve extrapolated from zero to infinity for total etoposide ($AUC_t$, in micrograms per milliliters per hour), expressing the level of systemic exposure to the total drug, was determined using the trapezoidal rule and estimation of the log-linear terminal slope according to the following formula:

$$AUC_t = \int_0^{\infty} C\,dt = \int_0^{24h} C\,dt + \int_{24h}^{\infty} C\,dt = AUC_{0-24} + C_{24}/\beta \ ,$$

where $\beta$ is the slope of the terminal exponential phase of a plot of log (drug concentration) versus time (this value is used to extrapolate the area from the last measured concentration to infinity). The area under the concentration-time curve extrapolated from zero to infinity for free etoposide ($AUC_f$ , in micrograms per milliliters per hour), expressing the level of systemic exposure to the free drug, was obtained by combination of $AUC_t$ and %PB as follows:

$AUC_f = AUC_t \times (100 - \%PB)$.

Bioavailability (F, in percent), expressing the fraction of an oral dose that actually reaches the systemic circulation, was calculated as:

$F = (AUC_{oral} \times D_{iv})/(AUC_{iv} \times D_{oral})$ ,

where $D$ is the dose in micrograms.

The mean residence time (MRT, in hours) was calculated as the ratio of the area under the first moment curve (AUMC) to the AUC using the formula:

$$MRT = \int_0^\infty t \times C\,dt_{iv} / \int_0^\infty C dt_{iv} = AUMC_{iv}/AUC_{iv} .$$

The effective half-life ($t_{1/2\text{eff}}$, in hours) was obtained from the product of MRT times 0.693 (ln 2) as follows:

$t_{1/2eff} = 0.693 \times MRT_{iv}$ .

CL (liters per hour per square meter) was calculated after the intravenous dose as the ratio of the etoposide dose (in micrograms) to the $AUC_{iv}$ as follows:

$CL = D_{iv}/AUC_{iv}$ .

The apparent volume of distribution at steady state ($V_{ss}$, in liters per square meter) was calculated as the product of CL and MRT after a single intravenous bolus dose of the drug:

$V_{ss} = CL \times MRT$ .

$C_{max}$ (in micrograms per milliliter) was the peak concentration observed, and $T_{max}$ (in hours) was the time of peak concentration.

### Pharmacodynamics study

The main PD end point (hematological toxicity) was measured by WBC decrease (%). We compared the percentage of WBC decrease among patients with differing liver function (Child-Pugh score and bilirubinemia).

### Statistical analysis

All statistical analyses were performed by nonparametric tests because several parameters did not follow normal distribution. Patients' characteristics, liver function tests, and PK and PD parameters were compared among groups by the Mann–Whitney or Kruskal–Wallis tests as deemed appropriate.

## Results

### Patients

We studied 17 patients, including 16 men and 1 woman; their median age was 65 years (range 52–83 years) and their median performance status (PS) was 90 according to Karnofsky (range 60–100). The patients' characteristics are summarized in Table 1. The whole population was divided into two groups in accordance with bilirubin levels: group 1 (total bilirubin $\leq 1.2$ mg/dl) comprised ten patients and group 2 (total bilirubin $> 1.2$ mg/dl) consisted of seven patients. All patients had HCC and underlying cirrhosis (Child A, $n = 9$; Child B, $n = 6$; and Child C, $n = 2$). The etiology of the cirrhosis was alcoholic in most patients ($n = 12$), viral in 4 patients, and alcoholic-viral in 1 patient. Some patients had received prior treatment with radiation ($n = 2$) and/or various chemotherapy regimens ($n = 2$) and/or hormone therapy ($n = 2$); 10 patients had been pretreated with TACE. Creatinine values were normal in all but two patients (median 1.0 mg/dl, range 0.7–2.5 mg/dl).

### Hepatic function tests

Total bilirubin plasma levels yielded two groups. Table 2 shows the results of liver assessment (MEGX test and standard hepatic biochemistry), expressed as median values and ranges. Albuminemia (3.6 g/dl, 3.3–4.8 g/dl) was in the normal range for all patients, whereas the other hepatic function parameters were altered. In all, 6 patients had high PT indices (PT > 1.2), 10 patients had low MEGX values (MEGX < 40 ng/ml), and 14 patients had high GOT levels (> 40 IU/l). GOT values and PT indices were higher in group 2 than in group 1 (150 versus 47 IU/l and 1.21 versus 1.01, respectively), whereas MEGX levels were lower (19.8 versus 50.0 ng/ml). A marked difference was observed in bilirubin (2.8 versus 0.9 mg/dl), the cutoff parameter. According to the classic Child-Pugh score, patients in group 1 had mild or moderate liver dysfunction, whereas those in group 2 had moderate to severe liver failure.

### Pharmacokinetics

The etoposide concentration versus time profile displayed a biexponential decay. Figure 1 shows the etoposide plasma $C_t$ (mean values ± SE) observed at each time point in the two groups after an oral dose. The PK results (median values and ranges) are summarized in Table 3.

**Table 1.** Patients' characteristics[a] (*PS* performance status, *NS* not significant)

| | Patients (*n*) | Age (years) | PS (Karnofsky) | α-Fetoprotein (ng/ml) | Creatinine (mg/dl) | Creatinine CL (ml/min) |
|---|---|---|---|---|---|---|
| Normal value/range | | | 100 | 0.0–15.0 | 0.6–1.4 | 70.0–140.0 |
| *All patients* (bilirubin 0.5–5 mg/dl) | 17 | 65 (52–83) | 90 (60–100) | 447.4 (20.0–312,000.0) | 1.0 (0.7–2.5) | 81.7 (30.1–143.0) |
| *Group 1* (bilirubin ≤ 1.2 mg/dl) | 10 | 66 (53–83) | 90 (70–100) | 193.7 (20.0–55,800.0) | 1.0 (0.7–2.5) | 81.9 (30.1–143.0) |
| *Group 2* (bilirubin > 1.2 mg/dl) | 7 | 65 (52–73) | 70 (60–90) | 2115.0 (149.0–312,000.0) | 1.0 (0.8–1.6) | 81.1 (51.3–121.8) |
| *P* | | NS | 0.02 | NS | NS | NS |

[a] Results are expressed as median values (range)

**Table 2** Liver function parameters as determined in the 17 patients with HCC in cirrhosis[a] (*PT* prothrombin time, *NS* not significant)

| | Patients (*n*) | MEGX (ng/ml) | PT index | Serum albumin (g/dl) | Total bilirubin (mg/dl) | SGOT (IU/l) | Child-Pugh score (number of patients) |
|---|---|---|---|---|---|---|---|
| Normal range | | > 40 | 0.85–1.20 | 3.2–5.5 | 0.0–1.1 | 4.0–40 | |
| *All patients* (bilirubin 0.5–5 mg/dl) | 17 | 35 (15–87) | 1.12 (1.01–1.37) | 3.6 (3.3–4.8) | 1.2 (0.5–5.0) | 77 (24–700) | A $n = 9$<br>B $n = 6$<br>C $n = 2$ |
| *Group 1* (bilirubin ≤ 1.2 mg/dl) | 10 | 50 (20–87) | 1.05 (1.01–1.37) | 4.0 (3.3–4.8) | 0.9 (0.5–1.2) | 47 (24–197) | A $n = 8$<br>B $n = 2$ |
| *Group 2* (bilirubin > 1.2 mg/dl) | 7 | 20 (15–47) | 1.25 (1.21–1.34) | 3.4 (3.3–3.9) | 2.8 (1.5–5.0) | 150 (52–700) | A $n = 1$<br>B $n = 4$<br>C $n = 2$ |
| *P* | | 0.01 | 0.02 | NS | 0.0006 | 0.02 | |

[a] Results are expressed as median values (range)

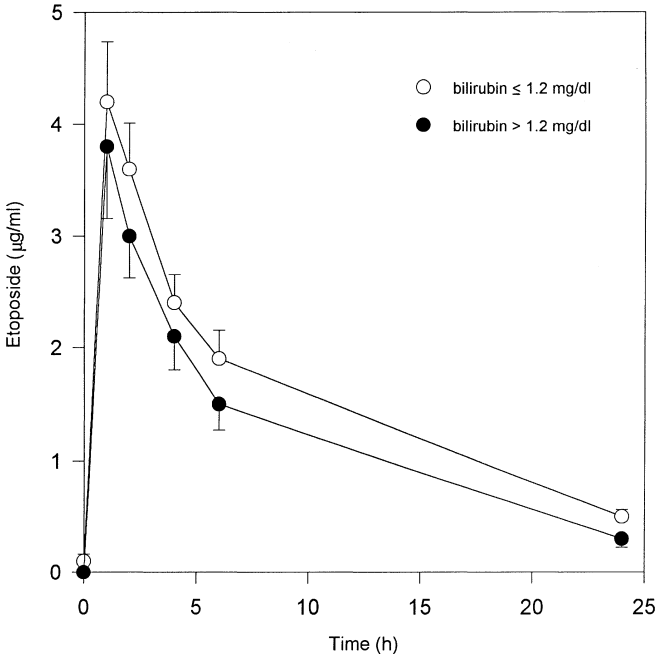


**Fig. 1** Concentration-time curves generated for total etoposide after an oral dose in the two groups of patients with HCC in cirrhosis (mean values ± SE)

As compared with data reported in the literature [17], our patients had normal or high etoposide F (61%, 17–95%), and normal $V_{ss}$ (8.4 l/m$^2$, 6.1–13.2 l/m$^2$) and $t_{1/2eff}$ (5.1 h, 3.0–9.6 h), whereas CL was normal or high (1.1 l h$^{-1}$ m$^{-2}$, 0.7–2.3 l h$^{-1}$ m$^{-2}$), especially in the seven jaundiced patients, resulting in a normal level of systemic exposure (27.0 µg h ml$^{-1}$, 8.4–56.0 µg h ml$^{-1}$; Fig. 1). Moreover, normal values for PB (93.2%, 84.4–98.1%) and exposure to free drug (1.9 µg h ml$^{-1}$, 0.6–5.9 µg h ml$^{-1}$) were found. When the two groups were considered separately, $C_{max}$, F, $AUC_{oral}$, PB, $AUC_{f,oral}$, and $V_{ss}$ values were similar in the two groups. A shorter MRT and $t_{1/2eff}$, due to a slightly higher CL and lower $V_{ss}$, were observed in group 2 as compared with group 1. In conclusion, patients in the two groups had similar PK parameters.

### Pharmacodynamics

A total of 40 courses of etoposide were delivered (median 2, range 1–6). To compare the response and toxicity profiles of etoposide, we evaluated patients after the first or second course. In all, 15 patients were evaluable for toxicity. Hematological toxicity primarily involved leukopenia, which occurred in 47% of the population [grade 4 (G4), $n = 1$; G3, $n = 3$; G2, $n = 2$; and G1, $n = 2$], but thrombocytopenia also occurred in 29% of the population (G4, $n = 1$; G2, $n = 1$; and G1, $n = 3$), and anemia occurred in 82% of the population (G3, $n = 1$; G2, $n = 7$; and G1, $n = 6$). The other toxicities encountered were G2 mucositis ($n = 1$) and G2 ($n = 6$) and G1 ($n = 1$) infection.

The mean decrease in WBC was 47 ± 10% and 38 ± 5% in groups 1 and 2, respectively (NS; Fig. 2a). The mean decrease in WBC (41 ± 8%, 46 ± 11%, and 40 ± 2%) was not significantly different among patients with various Child-Pugh scores (A, B, and C, respectively; Fig. 2b). The only case of severe (G4) hematological toxicity (WBC decrease 95%) was observed in one elderly patient (83 years) with reduced glomerular filtration (creatinine CL 30.1 ml/min). This patient belonged to group 1.

No objective response was documented in the nine evaluable patients; seven patients had progressive disease and two patients had stabilization with a median duration of 3.3 months (range 2–5 months). The median overall survival was 2.5 months (range 1–15 months).

## Discussion

Our objective was to evaluate whether patients with HCC and liver dysfunction undergoing oral therapy

**Table 3** Etoposide PK as determined in the 17 patients with HCC in cirrhosis[a] (*PB* protein binding, *NS* not significant)

| | Patients (*n*) | $C_{max}$ (μg/ml) | $AUC_{oral}$ (μg h $ml^{-1}$) | $AUC_{oral,24h}$ (μg h $ml^{-1}$) | $AUC_{iv}$ (μg h $ml^{-1}$) | $AUC_{iv,24h}$ (μg h $ml^{-1}$) | PB (%) | $AUC_{f,oral}$ (μg h $ml^{-1}$) | $AUC_{f,iv}$ (μg h $ml^{-1}$) | CL (l $h^{-1}$ $m^{-2}$) | $V_{ss}$ (l/$m^2$) | MRT (h) | $t_{1/2eff}$ (h) | F (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference values [17] | | | | | | | 94 | | | 0.9–2.1 | 7–17 | | 4–8 | 25–75 |
| *All patients* | 17 | 3.9 | 27.0 | 27.0 | 25.0 | 24.1 | 93.2 | 1.9 | 1.8 | 1.1 | 8.4 | 7.4 | 5.1 | 61 |
| (bilirubin 0.5–5 mg/dl) | | (1.7–6.9) | (8.4–56.0) | (8.4–48.5) | (12.0–40.0) | (12.0–35.8) | (84.4–98.1) | (0.6–5.9) | (0.6–4.2) | (0.7–2.3) | (6.1–13.2) | (4.4–12.6) | (3.0–9.6) | (17–95) |
| *Group 1* | 10 | 4.5 | 38.8 | 34.1 | 28.2 | 27.3 | 93.4 | 2.3 | 1.8 | 1.0 | 8.5 | 8.1 | 5.8 | 65 |
| (bilirubin ≤ 1.2 mg/dl) | | (2.0–6.7) | (8.4–49.0) | (8.4–48.5) | (15.0–40.0) | (15.0–35.8) | (87.8–98.1) | (0.6–5.9) | (0.6–4.2) | (0.7–1.6) | (6.1–13.2) | (6.8–13.8) | (4.7–9.6) | (17–92) |
| *Group 2* | 7 | 3.6 | 25.0 | 25.0 | 22.0 | 22.0 | 92.5 | 1.7 | 1.6 | 1.3 | 7.3 | 5.5 | 3.8 | 53 |
| (bilirubin > 1.2 mg/dl) | | (1.7–6.9) | (9.0–41.0) | (9.0–38.6) | (12.0–28.0) | (12.0–28.0) | (84.4–93.7) | (0.9–2.6) | (0.8–2.2) | (0.8–2.3) | (7.0–12.2) | (4.4–12.6) | (3.0–8.7) | (33–95) |
| *P* | | NS | NS | NS | 0.04 | 0.05 | NS | NS | NS | NS | NS | 0.03 | 0.03 | NS |

[a] Results are expressed as median values (range)




**Fig. 2a,b** Comparison of WBC decrease (%, expressed as mean values ± SE) data in patients with **a** normal bilirubin (≤1.2 mg/dl) and abnormal bilirubin levels (> 1.2 mg/dl) and **b** Child-Pugh A, B, and C cirrhosis

with etoposide would require a dose adjustment because of liver disease. This condition may affect the PK of etoposide and the PD consequences of its administration such that conventional doses could produce worse toxicity in patients with liver failure [6]. To address these issues we investigated the PK and PD of standard doses of etoposide in the above-mentioned patients. In particular, we dwelt upon drug disposition and protein binding. One would expect a decrease in CL as well as an increase in systemic exposure secondary to lower metabolism and/or biliary excretion because of reduced hepatic mass. Moreover, an increase in the unbound fraction of drug due to hypoalbuminemia and hyperbilirubinemia would be expected. This would have increased the level of systemic exposure to the free drug, which is responsible for PD effects, primarily adverse side effects. Despite these expectations, we found that the CL and protein binding of etoposide were normal and, more generally, that the PK was maintained even in patients with the most altered hepatic function, or, rather, that elimination of the drug was not slowed down. Indeed, we found a decrease in MRT, $t_{1/2eff}$, $AUC_{iv}$, and $AUC_{iv,24h}$ due to the slightly higher CL and lower $V_{ss}$ in patients with liver dysfunction, suggesting even an enhanced elimination of the drug in these

**Table 4** PK of etoposide in patients with liver dysfunction: comparison with previously published data (mean)

| | Our data | D'Incalci et al. [5] | Arbuck et al. [1] | Hande et al. [11] | Stewart [20] |
|---|---|---|---|---|---|
| Bilirubin | >1.2 mg/dl | >1.2 mg/dl | >1.0 mg/dl | >2 mg/dl | ≥1.0 mg/dl |
| Number | 7 | 15 | 8 | 11 | 6 |
| CL (l $h^{-1}$ $m^{-2}$) | 1.4 | 1.7 | 1.3 | 1.5 | 1.6 |
| $V_{ss}$ ($l/m^2$) | 8.4 | 12.2 | 9.6 | 12.4 | – |
| $t_{1/2}$ (h) | 4.6 | 4.9 | 7.3 | 5.7 | – |
| Free fraction (%) | 8.2 | – | – | – | 27 |
| Bilirubin | ≤1.2 mg/dl | <1.2 mg/dl | ≤1.0 mg/dl | <1.4 mg/dl | <1.0 mg/dl |
| Number | 10 | 18 | 9 | 23 | 15 |
| CL (l $h^{-1}$ $m^{-2}$) | 1.0 | 1.4 | 1.2 | 1.6 | 1.1 |
| $V_{ss}$ ($l/m^2$) | 9.2 | 11.4 | 9.5 | 13.7 | – |
| $t_{1/2}$ (h) | 6.2 | 5.6 | 8.1 | 6.4 | – |
| Free fraction (%) | 7.3 | – | – | – | 9 |

patients. In accordance with this PK finding, toxicity data were not particularly severe in these patients.

In a previous study we showed that even for vinorelbine, a drug mainly eliminated by the liver, CL is not modified in patients with mild or moderate liver involvement [16]. The CL of vinorelbine was strongly correlated with the MEGX value and was reduced only in patients with major (≥ 75%) liver involvement. In the present study, our data confirm the findings of D'Incalci et al. [5], Arbuck et al. [1], and Hande et al. [11], who showed that total etoposide clearance ($CL_t$) was not significantly altered in patients with hepatic impairment (i.e., hyperbilirubinemia) as compared with controls, even when this was associated with obstructive jaundice (Table 4). They agreed that these patients appeared to compensate for a slight reduction in the metabolic/biliary CL of etoposide with an increase in its renal CL.

We classified the liver dysfunction of our patients using bilirubinemia as a cutoff parameter because, among the numerous indices of liver assessment, hyperbilirubinemia is widely considered a sign of severe liver impairment in patients with cirrhosis [6]. In our patients this parameter suitably reflected the severity of hepatic dysfunction since the other hepatic function tests (except albumin, which was normal in all the patients) also went in the same direction; group 1, with normal bilirubin values (≤ 1.2 mg/dl), showed normal MEGX values and PT indices and slightly altered GOT levels, whereas group 2, with abnormal bilirubin values (>1.2 mg/dl), showed alterations in all these tests, especially MEGX and GOT. Group 1 had a majority of patients with Child A cirrhosis, whereas group 2 had a majority of patients with Child B cirrhosis and two patients with Child C cirrhosis. We found normal and similar PK results in the two groups (mild to severe liver impairment); therefore, in accordance with the above-mentioned investigators [1, 5, 11], we found no indication for a reduction in etoposide dose on the basis of liver function alone.

Stewart et al. [20] have shown that a decrease in etoposide $CL_t$ is not observed in patients with abnormal total bilirubin levels because the concomitant increase in unbound etoposide offsets the reduction in intrinsic free CL. These authors point out that although $CL_t$ does not significantly change in patients with increased bilirubin and/or low albumin values, the unbound etoposide fraction is higher due to lower degrees of protein binding. Moreover, they observed that the patients with hyperbilirubinemia had a higher fraction of unbound etoposide, elevated levels of systemic exposure to the unbound drug, and greater toxic effects (decrease in WBC) [21]. These data would support a dose reduction in patients with liver failure, even though $CL_t$ is not impaired [20]. In accordance with these observations, Joel and associates [12] have shown that increased hematological toxicity after etoposide administration to patients with abnormal organ function is mediated by an increase in etoposide $AUC_f$ and, therefore, that a dose reduction may be needed in such patients. We did not find an increase in the free etoposide fraction in our patients or in the jaundiced patients. This finding was confirmed by the occurrence of hematological toxicity in patients with normal bilirubin levels as well as in those with abnormal bilirubin values. This apparent contrast between our findings and Stewart et al.'s data might stem from differences in the patients' characteristics. Two of Stewart et al.'s patients had definitely higher bilirubin levels than did ours (≥ 20 mg/dl) and, together with another four of them, had albumin levels below the normal value (<3.2 g/dl). In our patients, serum albumin was in the normal range and the bilirubin level was altered, but within 5.0 mg/dl. Another explanation for this contrast might lie in the methodology of the protein binding study. We used in vivo measurement of PB% via ultrafiltration of the peak plasma samples of the patients, whereas Stewart et al. [20] used an ex vivo technique involving spiking of a blank plasma sample of the patients with etoposide.

Renal excretion, hepatic metabolism, and protein binding are the most important factors involved in etoposide elimination, and if one or more of them are affected, potentially the pharmacological effect is affected as well [18]. In our study, etoposide CL and protein binding were normal, resulting in a normal degree of exposure to free etoposide in spite of good bioavailability. The classic and dynamic hepatic function tests, except for albumin, produced altered results in the majority of our patients, indicating a real liver

impairment. MEGX levels, PT indices, and GOT values were abnormal in most patients, especially the jaundiced ones. An altered MEGX level reflects a reduction in intrinsic enzymatic activity. Observing the data in our hands, we can assert that whenever renal function is normal the CL of etoposide is normal, even if there is liver impairment. Indeed, our two patients with reduced CL (0.9 and 0.76 l $h^{-1}$ $m^{-2}$) also displayed lower creatinine CL (39.7 and 30.1 ml/min). Renal excretion is probably the most important pathway in etoposide disposition. Good renal CL makes up for the possible reduction in hepatic CL. Systemic elimination is affected only if glomerular filtration is decreased. Moreover, our data show not only that the PK of etoposide is maintained in patients with liver dysfunction but also that no important toxicity occurs. The only case of severe (G4) hematological toxicity was seen in one of the two patients with reduced glomerular filtration (creatinine CL 30.1 ml/min).

In conclusion, our data show that hepatic impairment due to HCC in cirrhosis does not alter etoposide disposition if the former is not associated with renal failure. CL and PB are not altered when albuminemia is normal and bilirubinemia does not exceed 5 mg/dl. This results in a normal level of systemic exposure to the free drug. Since the pharmacological effects of etoposide correlate with the level of systemic exposure to the unbound drug [12], there is no PK rationale for a reduction in dose for these patients. If their PS and bone marrow reserve are good, the dose intensity can even be increased under close therapeutic drug monitoring and hematological monitoring.

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