Feasibility study and pharmacokinetics of low-dose paclitaxel in cancer patients with severe hepatic dysfunction

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The aim of this study is to investigate the feasibility and determine the pharmacokinetics of low-dose paclitaxel in cancer patients with severe hepatic dysfunction. This was a prospective study. Patients with liver metastases who had either transaminase serum levels higher than 10 times the upper normal limit or bilirubin serum levels higher than 5 times the upper normal limit were eligible. All patients underwent pharmacokinetic evaluation during the first course of treatment. Pharmacokinetics in severe hepatic dysfunction patients were compared with data from a reference group of patients with normal hepatic function who participated in a phase I study. Nine severe hepatic dysfunction patients were treated with paclitaxel 70 mg/m^2 administered as a 1-h infusion every 2 weeks. They received a median three treatment courses (range 1–9) without clinically relevant toxicity. The area under the concentration–time curve of paclitaxel was markedly higher in severe hepatic dysfunction patients when compared with the normal hepatic function control group treated with the same dose (98% increase, $P<0.001$). Area under the concentration–time curve and the time above 0.1 μmol/l ($T>0.1$) concentration threshold in the severe hepatic dysfunction patients who received paclitaxel 70 mg/m^2 approximated pharmacokinetics of paclitaxel in patients with normal liver function who received 130 mg/m^2. Maximum plasma concentration (C_{max}) did not differ between the two groups. In conclusion, paclitaxel 70 mg/m^2 was safely delivered every 2 weeks in patients with severe hepatic dysfunction and resulted in adequate plasma concentrations. Paclitaxel at this dosage can be taken as an option for severe hepatic dysfunction patients who are expected to get clinical benefits from taxanes. *Anti-Cancer Drugs* 17:1219–1222 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:1219–1222

Keywords: liver dysfunction, paclitaxel, pharmacokinetics

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Received 5 June 2006 **Accepted** 3 July 2006

Introduction

Paclitaxel, the prototype of the taxane family, is an anticancer drug of particular interest because of its antitumor activity against a broad spectrum of malignant solid tumors, including breast, lung and ovarian cancer [1].

Paclitaxel is primarily metabolized in the liver by cytochrome P450 oxidative enzymes CYP2C8, CYP3A4 and CYP3A5, and a decrease of its clearance is likely in cases of liver dysfunctions [2–4]. It has been suggested that the reduced metabolic capacity of dysfunctioning liver is probably associated to the decrease of cytochrome enzymes at the hepatic level [5]. In keeping with that, Jiko *et al.* [6] demonstrated that clearance of paclitaxel was reduced by 73% and CYP3A activity by 92% following induction of hepatic failure in preclinical models. Therefore, a dosage adjustment is required when considering its therapeutic application in patients with abnormal liver function. Owing to the lack of relevant clinical studies, administration of paclitaxel is not recommended for patients who have either transaminase serum levels higher than 10 times the upper normal limit (UNL) or bilirubin serum levels higher than 5 times the UNL [7].

To contribute to the management of this population of patients, we conducted a clinical and pharmacological study with the aim to investigate the feasibility and determine the pharmacokinetics of low-dose paclitaxel in cancer patients with severe hepatic dysfunction (SHD).

Methods

Subjects

This study was conducted at the Medical Oncology Department of the Ioannina University Hospital, Greece from March 2001 to November 2003. The study had the approval of the local Medical Ethics Committee and a witnessed informed consent was obtained from all patients prior to study entry. Nine patients with SHD, attributed to cancer metastases of the liver, entered the study (Table 1). They had refractory metastatic tumors and presented with either transaminase levels higher

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Table 1 Demographics

Patients entered	9
male	6
female	3
Age	
median	57
range	48–73
Performance status	
median	2
range	1–2
Prior chemotherapy	0
Primary sites	
CUP	3
pancreatic	3
cholangiocarcinoma	3

CUP, cancer of unknown primary.

Table 2 Baseline liver biochemistry in patients with SHD

	Bilirubin (× UNL)	AST (× UNL)	ALT (× UNL)	ALP (× UNL)	γ-GT (× UNL)	Albumin (g/dl)
Median	7.5	3	3.5	7	10	3.1
Range	3–11	2–12	2–8	4–30	5–20	2.8–4

UNL, upper normal limit; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphate; γ-GT, γ-glutamyl transferase.

than 10 times the UNL or bilirubin serum levels higher than 5 times the UNL at study entry. Baseline liver biochemistry tests are shown in Table 2. Other inclusion criteria included age between 18 and 75 years, performance status 0–2 on the World Health Organization scale, adequate heart function, adequate bone marrow documented by a white blood cell count $\geq 3.5 \times 10^9$/l, an absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 150 \times 10^9$/l and serum creatinine within normal limits. Patients were also required to have negative tests for hepatitis B surface and hepatitis C antigens.

Treatment

SHD patients received paclitaxel 70 mg/m^2 administered by 1-h intravenous infusion. Standard premedication was administered in all patients: methylprednisolone 16 mg orally at 12 and 2 h before paclitaxel, and dimetindene maleate 0.1 mg/kg and ranitidine 50 mg given intravenously 30 min before paclitaxel, to prevent hypersensitivity reactions. Ondansentron 8 mg was the standard prophylactic antiemetic treatment used in all cases. Cycles were repeated at 2-weekly intervals. Hematological and biochemistry assessments were performed in all patients on a weekly basis.

Sampling

Blood sampling for pharmacokinetics was performed during the first administration of paclitaxel in all patients. A second sampling was optional in patients who managed to receive at least four courses of treatment. The blood samples were taken before the start of paclitaxel infusion, at the end of the infusion, at 15, 30 and 45 min, and 2, 4, 6 and 24 h after the end of the infusion. Five-milliliter blood samples were collected in heparinized tubes from an indwelling intravenous catheter set in the arm not used for the treatment infusion. Samples were centrifuged after withdrawal for 5 min at 3000 r.p.m. and 4°C, and separated plasma was stored in polypropylene vials at –20°C until analysis.

Bioanalysis

Samples were analyzed for total plasma paclitaxel at the Laboratory of Analytical Chemistry, European Environmental Research Institute, Ioannina, Greece. The plasma concentrations of paclitaxel were determined by a high-performance liquid chromatographic method that has been described in detail elsewhere [8]. The validated quantitation range was 10–1000 ng/ml paclitaxel (0.012–1.17 μmol/l) in plasma and the coefficient of variation was $< 9\%$.

Pharmacokinetics

Pharmacokinetic evaluations were based on the real blood sampling times documented on the respective forms. Noncompartmental pharmacokinetic calculations were performed with the WinNonlin version 2.1 program (Pharsight, Palo Alto, California, USA). The area under concentration–time curve from time zero to the infinity (AUC_{INF}) was computated by using the linear trapezoidal rule from time zero to the time corresponding to last sampling point (C_{last}) and extrapolation to infinity, based on the last observed concentration. The duration of paclitaxel plasma concentrations above 0.1 μmol/l (90 ng/ml), which has been shown to be associated with hematological toxicity and objective response in patients with advanced cancers, was calculated directly from the AUC_{INF} graph [9–11].

Statistical analysis was performed and computed with the Prism 4 for Windows program (GraphPad Software, San Diego, California, USA). Pharmacokinetics in SHD patients was compared with those obtained in a reference population of patients with normal hepatic function (NHF) who participated in a phase I study [12]. We used the Wilcoxon matched-pairs nonparametric test and two-tailed P values were determined. P values less than 0.05 were considered statistically significant.

Results

Clinical data

A total of nine patients received 33 biweekly infusions of paclitaxel (median 3, range 1–9). Treatment was discontinued due to disease progression in all cases. Two patients, one with cholangiocarcinoma and one with cancer of unknown primary, uneventfully received nine and five biweekly treatment courses, respectively. Toxicity was mild. The worst hematological toxicity was leucopenia grade I recorded in three cases 7 days after first treatment administration. Otherwise only alopecia

grade I occurred in a patient who had nine infusions of paclitaxel administered. Cumulative toxicity was not assessable because of the overall short duration of treatment in this SHD group of patients.

Pharmacokinetics

Median values of pharmacokinetics are shown in Tables 3 and 4. In patients with normal liver function, AUC_{INF} increased with increasing doses. Median AUC_{INF} values in these patients ranged from 1521 ng h/ml in patients treated at 70 mg/m^2 up to 5238 ng h/ml in patients treated at 130 mg/m^2. The time above 0.1 µmol/l ($T_{>C0.1}$) threshold concentration for paclitaxel was 4–12 h in patients treated at 70 and 90 mg/m^2 and up to 30 h in patients who had received paclitaxel 130 mg/m^2.

Pharmacokinetic values obtained in SHD patients were significantly different when compared with control group patients with normal liver function who received the same dosage of paclitaxel (70 mg/m^2). The AUC_{INF} was higher (median value 3000 vs. 1521 ng h/ml, $P = 0.02$), systemic clearance was lower (23 vs. 46 l/h, $P = 0.03$) and terminal half-was life higher (4.2 vs. 1.6 h). The median time above paclitaxel threshold concentration of 0.1 µmol/l ($T_{>C0.1}$) in SHD patients was 9 h (range 4.5–12.5 h) compared with 4.25 h (range 3–5.5) in the NHF patients. Although the median maximum plasma concentration of paclitaxel was higher in the liver impairment group (1732 vs. 1082 ng/ml/week), this difference did not reach statistical significance. Figure 1 illustrates change of paclitaxel plasma concentrations in a patient with cholangiocarcinoma who achieved near-normal levels of liver enzymes and bilirubin after five courses of treatment.

Table 3 Pharmacokinetics in SHD patients treated with paclitaxel 70 mg/m^2

Patients	C_{max} (ng/ml)	Cl (l/h)	AUC_{INF} (ng h/ml)	$T > 0.1$ mol/l (h)	$T_{1/2\lambda z}$ (h)
1	1732	18	8860	12,5	6.5
2	1765	32	2185	7	0.5
3	1321	25	2755	7	2
4	1279	40	1740	9	1.2
5	600	9	5180	15	11.3
6	580	40	1700	9	6
7	2855	16	4412	7	4.2
8	2930	15.3	4581	11	4.5
9	2252	23	3000	4,5	1

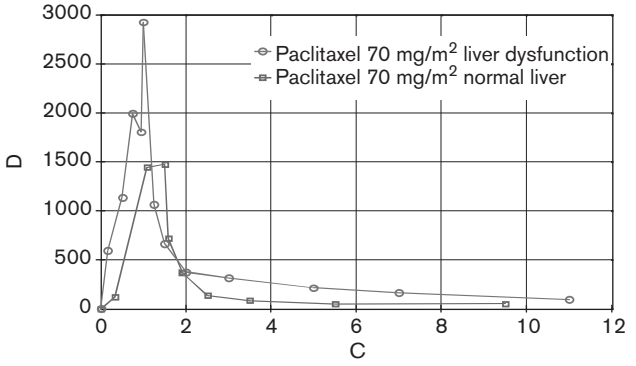
SHD, severe hepatic dysfunction; AUC_{INF}, area under the concentration–time curve.

Table 4 Median pharmacokinetic parameters of paclitaxel in patients with normal liver function

Dose level (mg/m^2)	AUC (ng h/ml)	Cl (l/h)	C_{max} (ng/ml)	$T_{1/2\lambda z}$ (h)	$T > 0.1$ mol/l (h)
70	1521	46	1082	1.6	4.25
90	1692	54	855	3.8	4
130	5238	32	4532	2	7.5

AUC, area under the concentration–time curve.

Fig. 1



Concentration–time curve of paclitaxel dosed at 70 mg/m^2 in a patient with cholangiocarcinoma when initially treated at a SHD status and again at the sixth course when his liver enzymes and bilirubin subsided back to near normal values. SHD, severe hepatic dysfunction.

Discussion

Dose adjustment is a rule for drugs that are metabolized in the liver because hepatic function can have a major impact on their pharmacokinetics and pharmacodynamic behavior [13,14]. This is also the case for paclitaxel that is eliminated by hepatic metabolism and billiary excretion [2,15]. Despite the widespread clinical use of this therapeutic, there is limited data available to support appropriate dose adjustments in patients with slight to moderate hepatic dysfunction. For patients with SHD no data exist. This is due to established research practices according to which patients with near-end organ dysfunctions are excluded from clinical trials [7,16]. We conducted this prospective study with the aim to provide useful information on the pharmacokinetics and tolerability of paclitaxel in this special population of cancer patients.

We used liver enzymes and bilirubin serum concentration values as determinants of the status of liver function when eligibility criteria were considered for this study. Despite a lack of specificity in determining liver function status, these tests are commonly used by physicians to characterize liver function status from an empirical point of view [17]. Otherwise, the lack of widely acceptable accurate tests and the heterogeneity of participants would further hamper the conduct of clinical pharmacological studies in this clinical setting [18].

The differences in pharmacokinetics, obsereved among patients with NHF and those with SHD, suggest that a

slower elimination rate in patients with SHD makes the difference. This is apparent when considering median times of detectable plasma concentrations and time above paclitaxel threshold concentration of 0.1 μmol/l. Overall pharmacokinetic values obtained in SHD patients who received paclitaxel 70 mg/m^2 approximated somehow those in NHF patients who received paclitaxel 130 mg/m^2.

We found a substantial interindividual variability in pharmacokinetics of paclitaxel in our population. These findings indicate that the effects of hepatic insufficiency on the pharmacodynamics of paclitaxel are neither consistent nor predictable. Most likely explanations are the variety of liver dysfunction among studied persons and possibly a genotypic variability of cytochrome P450 enzymes [4]. Moreover, the median plasma albumin in SHD patients might have also contributed to the pharmacokinetic variability in this cohort of patients, given that hypoalbuminemia may result in more free drug available into the circulation [19]. Nevertheless, it must be emphasized that a 70-mg/m^2 dose of paclitaxel was proven safe in this heterogeneous group of cancer patients with SHD.

We acknowledge the small number of patients as a major weakness of this study. These data, however, have potential applicability because they can guide dosing of paclitaxel in cancer patients with advanced liver dysfunction, who are expected to get clinical benefit from this agent. According to our knowledge, there is only one study published that deals with paclitaxel in liver dysfunction [20]. In that study, 81 patients were enrolled, but only nine patients in the 24-h infusion schedule and 12 patients in the 3-h infusion schedule had advanced hepatic dysfunction defined by bilirubin higher than 3 mg/dl. Definite recommendations for dose adjustment were not provided in that study because of the large heterogeneity of patient population and variability of liver function.

We conclude that hepatic dysfunction has a major impact on the pharmacokinetics and pharmacodynamics of paclitaxel. Paclitaxel 70 mg/m^2, however, can safely be administered every 2 weeks in cancer patients with SHD and may achieve adequate plasma concentrations.

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