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Phase I trial and pharmacological study of a 3-hour paclitaxel infusion in children with refractory solid tumours: a SFOP study

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Summary The maximum tolerated dose of paclitaxel administered by 24-hour continuous infusion in children is known. Short infusion might offer equivalent antitumour efficacy and reduced haematological toxicity, without increasing the allergic risk. Our aims were to determine the maximum tolerated dose and the pharmacokinetics of paclitaxel in children when administered in 3-h infusion every 3 weeks. Patients older than 6 months, younger than 20 years with refractory malignant solid tumours were eligible when they satisfied standard haematological, renal, hepatic and cardiologic inclusion criteria with life expectancy exceeding 8 weeks. Paclitaxel was administered as a 3-hour infusion after premedication (dexamethasone, dexchlorpheniramine). Pharmacokinetic analysis and solvent assays (ethanol, cremophor) were performed during the first course. 20 courses were studied in 17 patients; 4 dosage levels were investigated (240 to 420 mg/m^2). No dose-limiting haematological toxicity was observed. Severe acute neurological and allergic toxicity was encountered. One treatment-related death occurred just after the infusion at the highest dosage. Delayed peripheral neurotoxicity and moderate allergic reactions were also encountered. Pharmacokinetic analysis showed dose-dependent clearance of paclitaxel and elevated blood ethanol and Cremophor EL levels. Although no limiting haematological toxicity was reached, we do not recommend this paclitaxel schedule in children because of its acute neurological toxicity. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: paclitaxel; short-term infusion; phase 1; children

Paclitaxel is an anti-microtubular agent with a known efficacy in numerous adult solid tumours (Rowinsky and Donehower, 1995). A phase I trial of paclitaxel in children with refractory solid tumours showed that the recommended dose for phase II trials was 350 mg/m^2 day^{-1} when administered as a 24-hour infusion. The main dose-limiting toxicity was neurological (peripheral neuropathy in one patient, tonic-clonic seizure in another). The other toxicities encountered were expected from adult experience: haematological toxicity, hypersensitivity (Hurwitz et al, 1993). However, some clinical data support the fact that a 3-hour short-term infusion of paclitaxel might offer equivalent anti-tumour efficacy and reduced haematological toxicity without increasing the risk of hypersensitivity (Eisenhauer et al, 1994). Phase I trials in adults of paclitaxel administered as a 3-hour infusion showed that the recommended dose for solid tumours was 210 mg/m^2 or 250 mg/m^2 with G-CSF support (Schiller et al, 1994; Younes et al, 1995).

Despite the usual remarkable chemosensitivity of malignant solid tumours in children, the development of new agents or new methods of drug administration with demonstrated efficacy and acceptable toxicity is still justified for refractory or relapsed tumours. The aim of this study was to determine the dose-limiting toxicity, maximum tolerated dose and pharmacokinetics of paclitaxel in children when administered as a 3-hour infusion. Since paclitaxel has low water solubility, it is formulated for clinical use in 50% cremophor EL and 50% ethanol, so that patients receiving paclitaxel therapy also receive a significant amount of these solvents. Because of the toxicity encountered, we also investigated the pharmacokinetics of these two solvents.

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PATIENTS AND METHODS

Eligibility

Patients older than 6 months and younger than 20 years at the time of treatment with histologically documented malignant solid tumours, refractory to at least two lines of conventional therapeutic modalities with a life expectancy of more than 8 weeks were eligible for the study, provided they satisfied the following eligibility criteria: Lansky score ≥50 (Lansky et al, 1987), adequate haematological status (Granulocytes ≥1000 µl^{-1}, platelets ≥100 000 µl^{-1} except in the case of bone marrow involvement), normal liver function (bilirubin 1.25 × N, AST and ALT 2 × N, fibrinogen 1.5 g l^{-1} and prothrombin level ≥60%), adequate renal function (creatinine < 100 µmol l^{-1}, creatinine clearance ≥70 ml min^{-1}/1.73 m^2), normal electrocardiogram and

echocardiography and no organ toxicity with WHO grade >2. In patients with epilepsy, the plasma level of the antiepileptic drug had to be within the therapeutic range. No other anticancer treatment was allowed during the study and the time interval between previous treatments and administration of paclitaxel had to be at least 3 weeks and 6 weeks in the case of previous use of nitrosoureas.

A patient could not be included in the case of severe infection, previous large field irradiation (such as craniospinal irradiation), previous use of high-dose chemotherapy with haematopoietic stem cell transplantation, known heart disease, previous neurological toxicity grade ≥2, disseminated hepatic metastases and known allergy to cremophor (e.g. previous allergy to teniposide). The protocol was approved by ethical committee and by participating institutions. Written informed consent was obtained from parents, guardians and children when appropriate.

Treatment

Paclitaxel was supplied by Bristol Myers Squibb (Paris La Défense, France) as a concentrated sterile solution in 50% poly-oxy-ethylated castor oil (cremophor EL) and 50% dehydrated ethanol. Paclitaxel was diluted to a final concentration of 0.3 to 1.2 mg ml^{-1} in 5% dextrose in water before administration over 3 hours with cardiac monitoring. Premedication was performed using dexamethasone (0.25 mg kg^{-1}, 12 and 6 hours before infusion) and dexchlorpheniramine (2.5 to 5 mg according to age) 30 minutes before infusion. No H2-blocking agent was used. The starting dose of paclitaxel was 240 mg/m^2 taking into account the recommended dose in adults for short-term infusion (Schiller et al, 1994) as well as the recommended dose in children for 24 hours infusion (Hurwitz et al, 1993). Dose escalation was planned with 20% increments: second step 290 mg/m^2, third step 350 mg/m^2, and fourth step 420 mg/m^2. A minimum of 3 patients was included at each step. There was no intra-patient dose escalation.

Toxicity

Toxicity criteria were assessed after the first course, according to NCl-CTC and WHO definitions respectively. Toxicity was assessed after each course but dose-limiting toxicity was only assessed after the first course. The dose-limiting toxicity criteria were: persistence of grade IV neutropenia or thrombocytopenia for more than 7 days, any grade IV non-haematological toxicity, any grade III neurotoxicity, any grade III non-haematological toxicity except grade III nausea, grade III transitory hepatotoxicity, grade III fever and grade III mucositis. If at least two or more patients at a given dose level encountered one of these criteria, the dose-limiting toxicity (DLT) was reached and 3 additional patients were included to be treated at the dose level preceding the DLT.

Clinical examination, full blood count, liver, renal and electrolyte values, chest X-ray and antiepileptic drug assay, when applicable, were performed before each course. Haematological toxicity was assessed by at least 3 full blood counts per week. Except in the case of clinical evidence of disease progression after one course, tumour evaluation was planned to be performed every two courses. Patients could receive additional courses at 3-week intervals except in the case of disease progression or stable disease after 2 consecutive courses or dose-limiting toxicity. The eligibility criteria for further courses were the same as for the first course. The planned interval between two courses was 21 days with a maximum interval of 35 days.

Pharmacokinetic studies

Blood samples were drawn before treatment and at 12 time points during and for up to 72 hours after infusion (90 and 180 minutes after the beginning of infusion; 10, 30, 60 minutes and 2, 4, 6, 12, 24, 48 and 72 hours after the end of infusion). Plasma was obtained by centrifugation and frozen at -20°C; 50µl to 1 ml of patient plasma were assayed for total paclitaxel determination by a validated high-performance liquid chromatography method (Martin et al, 1998). The limit of quantification was 25 ng ml^{-1} (29 nM). In plasma spiked with 44, 440 and 750 ng ml^{-1}, the interassay variability was 11.18%, 2.97% and 3.02%, respectively. Total area under the curve (AUC) was determined by the linear trapezoidal rule extrapolated to infinity. The terminal rate constant (β) was determined by log-linear least-squares fit of the terminal elimination phase. Total-body clearance was calculated by dividing the dose by AUC. The C_{max} sample was drawn at the end of infusion. Duration of threshold above 0.1 µM, which has been reported to be correlated with more severe neutropenia (Huizing et al, 1993; Gianni et al, 1995), has been determined in each patient. Plasma alcohol was assayed by a standard gas liquid chromatography method, using ethylacetate as internal standard. Cremophor EL levels were quantified by an HPLC method based on saponification of Cremophor EL, followed by extraction with chloroform and derivatization of the released fatty acid ricinoleic acid as described in detail previously (Sparreboom et al, 1996a) with minor modifications (Van Tellingen et al, 1999).

Correlation between observed toxicity and pharmacokinetic parameters of paclitaxel and solvents were studied.

Tumour response

Response evaluation was planned after 2 courses and tumour response was defined as follows: complete response, complete regression of all apparent tumour masses; partial response, >50% decrease in the product of the greatest perpendicular diameters of all measurable lesions without appearance of new lesions; and minimal response, >25% but less than 50% objective decrease in measurable tumour without other evidence of disease progression. Stable disease was defined as a less than 25% objective decrease in a measurable tumour without other evidence of disease progression. Progressive disease was defined as a more than 25% increase in any measurable tumour. Evaluation of tumour was not planned after one course but a second course was not administered in the case of obvious clinical progression or severe toxicity of the first course.

RESULTS

Patient population

Between February 1995 and November 1995, 17 patients were included in the study and 4 dosage levels were investigated (Tables 1 and 2). 14 patients received only one course because of tumour progression or toxicity and 3 patients received 2 courses. No patients received more than 2 courses. The patient population consisted of 6 females and 11 males with a median age of 9 years (range: 19 months–19 years). Diagnoses are described in Table 1.

11 patients were treated for primary refractory disease and 6 patients for relapse. One to 4 chemotherapy lines were used before treatment with paclitaxel (median = 3) (Table 1). 8 patients had also received previous localized radiotherapy. At the time of

Table 1 Patients characteristics

Characteristics	No of patients
Age, years	
Median	9
Range	1.6–19
Sex	
Male	11
Female	6
Tumour histology	
Rhabdomyosarcoma	7
Ewing's sarcoma	2
Neuroblastoma	2
Osteosarcoma	1
Hepatoblastoma	1
Nephroblastoma	1
Malignant glioma	1
Adrenocortical carcinoma	1
Kruckenberg tumour	1
No of prior therapy regimens	
0–2	5
3–4	12
Radiotherapy	6

treatment, Lansky score was 100 for 12 patients, between 60 and 80 for 5 patients with correct general status but reduced mobility due to the tumour and 50 for one patient because of paraplegia. Only one patient received an anti-epileptic drug (carbamazepine) with a blood concentration within therapeutic range before treatment.

Acute toxicity (Table 2)

We observed non-haematological dose-limiting toxicity in 2 patients after the first course at 420 mg/m^2 and another grade IV non-haematological toxicity in one patient after the second course at 350 mg/m^2. The first dose-limiting toxicity was observed in a patient who was included in the study for a refractory metastatic adrenocortical carcinoma treated with mitotane and hormonal substitution; her Lansky score was 100. She presented with nausea and headache 2 hours after starting the infusion followed by vomiting and diarrhoea during the third hour of infusion. No rash or oedema was observed. 30 minutes after the end of the infusion, she developed haemodynamic failure with brief cardiac arrest. She was rapidly managed with fluid modified gelatine, adrenaline and hydrocortisone hemisuccinate. Routine laboratory tests were performed while starting resuscitation and showed profound metabolic acidosis and no hypoglycaemia. Despite active management in the intensive care unit, she died as a result of multiorgan failure syndrome 12 hours after the start of paclitaxel infusion.

The other patient with dose-limiting toxicity had been included for a refractory malignant glioma and had a Lansky score of 100 before treatment. He developed transitory coma few minutes after the end of the infusion at 420 mg/m^2; there was no abnormal movement and the patient progressively recovered a normal level of consciousness within 4 hours. During the study, another patient experienced a similar neurological toxicity, but only after the second course. This patient, included at the 350 mg/m^2 level, was 19 months old and weighed 9.8 kg. Because of his young age and low weight, and because of the previous toxicity observed at the 420 mg/m^2 step, he received the first course at 2/3 of the theoretical dose (equivalent to 250 mg/m^2) and had not experienced any limiting toxicity. This patient then received a second course at the full dose level and we observed transitory coma following this second paclitaxel infusion. In both patients with transient coma, routine laboratory tests were performed. No hypoglycaemia was observed but transitory metabolic acidosis was found in both cases (pH 7.26 and 7.23; bicarbonate 16 and 8 mmol l^{-1} respectively); transient elevation of transaminases (5 × N) for 4 days in one of these 2 patients was also noted. Electro-encephalogram was performed in these 2 cases and showed no specific abnormality.

One grade I central nervous system toxicity was also observed with transitory alteration of consciousness in one patient receiving concomitant morphine dose escalation. In two patients, transitory grade I and II alteration of consciousness (anxiety or hypersomnia)

Table 2 Neurological and allergic toxicity after paclitaxel infusion

			Neurological toxicity				Allergic toxicity			
	Patient number	Dosage (mg m^{-2})	Acute	Grade	Delayed	Grade	Acute	Grade	Delayed	Grade
	201	290								
	202	290			paraesthesia	I			rash/pruritis	I
II	203	290			dysaesthesia	III			rash/pruritis	I
	204	290	mild agitation	I	excitation	I			rash/pruritis	I
	205	290								
	206	290								
	301	350	somnolence[b]	I						
IIIa	302	350			headache, ileus					
	303	350			and paraesthesia	II				
	311	250[a]								
IIIb	*311*	*350*	*coma*	*IV*						
	312	350	somnolence/agitation	II			mild pruritis	I	rash/pruritis	II
	401	420	coma	IV	dysaesthesia	III				
IV	402	420								
	403	420	coma/agitation	IV			anaphylactic collapse/death	IV		

Toxicity was assessed according to the NCI-CTC definitions. [a]Patient no. 311, step IIIB was 19 months old and weighed 9.8 kg: he received the first course at 2/3 of the theoretical dose (equivalent to 250 mg/m^2) and no limiting toxicity was observed. This patient then received a second course at the full dose level (line in *italics*) and transitory coma was observed following this second paclitaxel infusion. [b]patient no. 301: had morphine dose escalation just before paclitaxel infusion.

were noted during the infusion. No neurological toxicity was observed in the patient who received carbamazepine anticonvulsive therapy. Grade I or II nausea was observed in three courses at 290 and 350 mg/m^2.

Delayed toxicity (Table 2)

The observed haematological toxicity was not dose limiting. Grade IV neutropenia was observed twice at the 240 and 350 mg/m^2 dosage levels, with a duration less than 7 days, and grade III neutropenia was observed 5 times (at 290 and 350 mg/m^2). No grade IV leukopenia occurred; grade III leukopenia occurred 5 times at 240, 290 and 350 mg/m^2. No thrombocytopenia was encountered. Red blood cell transfusions were necessary in 4 courses for 3 patients receiving 290, 350 and 420 mg/m^2; 2 of these patients had an intra-tumour bleeding. Only one patient experienced documented infection with *Enterobacter* septicaemia during grade IV neutropenia (stage 4 neuroblastoma). 2 patients experienced transitory fever of unknown origin without neutropenia at 350 mg/m^2.

Delayed hypersensitivity reactions with skin rash and pruritis were observed 4 times at 290 and 350 mg/m^2. These symptoms persisted for 7 to 19 days. One case of pruritis was observed 24 hours after the end of the infusion, which then persisted for 19 days associated with skin rash (grade II). In one patient, at the 350 mg/m^2 dose, these symptoms occurred very intensively between days 10 and 15 after the infusion and required hospitalization and treatment with antihistaminic drugs, corticosteroids, benzodiazepine and morphine. Another patient presented paraesthesia and grade III pruritis, but without skin rash, between day 5 and day 15 after a 420 mg/m^2 infusion, requiring hospitalization and was successfully treated by clonazepam, sulpiride and corticosteroids: we interpreted these symptoms as a peripheral nervous system toxicity rather than an allergic reaction.

No mucositis was observed. One patient experienced grade I delayed vomiting at 290 mg/m^2. One patient experienced transitory grade II diarrhoea, two days after the infusion at 350 mg/m^2. One patient also experienced transitory ileus at 350 mg/m^2, but with concomitant increasing morphine dosage. No late renal or electrolyte abnormality was observed. Elevated transaminases 3 weeks after the infusion were recorded 3 times at the 290, 350 and 420 mg/m^2 dosage levels to values 2 to 13 times normal values. Alopecia was observed 3 times in 3 evaluable patients.

Pharmacokinetics and correlation with toxicity

Pharmacokinetic data were available for all 17 patients. The pharmacokinetic analysis of the 19-month-old patient who was included at the 350 mg/m^2 dose level but treated during the first course at 2/3 of the theoretical dose (equivalent to 250 mg/m^2 for a weight of 9.8 kg) was performed only during this first course: no pharmacokinetic analysis was performed during the second course at the full dose level associated with grade IV neurological toxicity. Selected pharmacokinetic parameters of paclitaxel are listed in Table 3 together with the C_{max} values for ethanol and cremophor. Figure 1 illustrates the typical pharmacokinetic profiles of paclitaxel at 290 mg/m^2. For each dose level, mean duration of paclitaxel plasma concentration threshold above 0.1 μM was respectively 21, 24, 30 and 34 hours. In our study, we observed high plasma alcohol levels after paclitaxel infusion: C_{max} values of ethanol ranged between 0.24 and 2.04 g l^{-1} (Table 3). Furthermore, the C_{max} concentrations of cremophor in plasma after paclitaxel infusions ranged between 6.12 and 22.37 g l^{-1} (Table 3). We retrospectively calculated that the amount of ethanol received by the patients over 3 hours ranged between 0.39 and 1.05 g kg^{-1} and the amount of cremophor ranged between 0.52 and 1.4 g kg^{-1}. Severe neurological toxicity was observed in both patients with the highest concentrations of ethanol and cremophor. 3 patients with coma and somnolence in whom ethanol concentration was measured have 3 of the 4 highest ethanol concentrations, above 1.45 g l^{-1}. No clear correlation of the toxicity with age was observed.

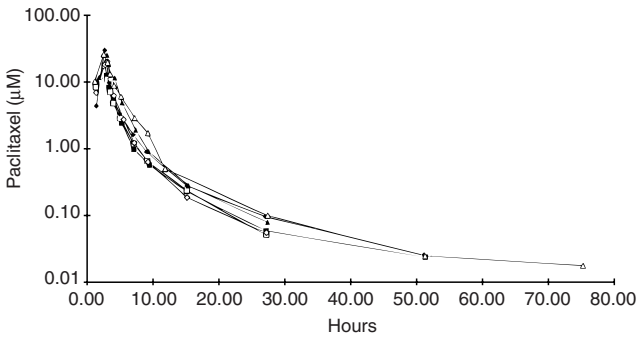

Figure 1 Plasma concentrations of paclitaxel in children treated with 290 mg/m^2 of paclitaxel as a 3-hour infusion

Table 3 Pharmacokinetics of paclitaxel in children after 3-hour infusion. Determination of C_{max} of the solvents, ethanol and cremophor. Means and standard deviation.

	Paclitaxel data					Alcool	Cremophor
Dose level mg/m^2	Cmax μM	Clexp L/h/m^2	AUCexp μMxh	T1/2elim H	Vβ L	C_{max} (g l^{-1})	C_{max} (g l^{-1b})
240	8.3[a]	8.48	33.8	7.23	140.8	0.40[a]	8.37[a]
	(2.1)	(1.24)	(4.8)	(1.34)	(31.1)	(0.15)	(2.05)
290	22.4	4.99	70.8	9.69	71.7	0.93	13.15
	(6.5)	(0.99)	(15.7)	(4.93)	(38.6)	(0.24)	(2.29)
350	40.2	3.39	156.7	5.23	19.2	1.17	16.9
	(17.8)	(1.61)	(75.7)	(1.36)	(9.1)	(0.39)	(3.4)
420	38.9[a]	2.74	179.6	10.24	39.4	1.6[a]	18.9[a]
	(4.9)	(0.01)	(0.1)	(0.8)	(8.3)	(0.38)	(3.6)

[a]C_{max} under-estimated in 2 cases because infusion duration greater than 3 hours. [b]1 g l^{-1} = 0.95 μl ml^{-1}

Tumour responses

Tumour response was evaluable in all patients, except for one case because of early death. One patient treated for embryonal rhabdomyosarcoma experienced a more than 50% decrease of an abdominal lymph node after one course at 350 mg/m^2, but treatment had to be stopped because of a delayed allergic reaction. Stable disease was observed after 2 courses at 350 mg/m^2 in one patient with alveolar rhabdomyosarcoma but the treatment had to be stopped because of a severe toxicity at the second course. For 2 other patients, we did not observe disease progression after one course but treatment had to be stopped because of severe toxicity. Disease progression was observed in the 12 other evaluable patients (10 after 1 course, 2 after 2 courses).

DISCUSSION

The haematological toxicity was not dose limiting in this study, despite high paclitaxel C_{max} and prolonged time of paclitaxel plasma levels above 0.1 μM which is usually correlated to more severe neutropenia (Huizing et al, 1993; Gianni et al, 1995). This low haematological toxicity, associated with apparent high drug exposure, might be due to a better haematological tolerance of paclitaxel in children than in adults. However, this might also be due to interference between the paclitaxel and cremophor EL pharmacokinetics: it has been recently reported that the higher plasma levels of paclitaxel do not reflect higher levels in tissues, since cremophor EL increases the affinity of paclitaxel to plasma components (Van Tellingen et al, 1999).

On the other hand, acute non-haematological toxicity was dose limiting and related to high C_{max} of paclitaxel, ethanol and cremophor EL. Severe acute toxicity were observed in 2 patients after the first course given at a dose of 420 mg/m^2 and also in an infant who received the full dose of 350 mg/m^2 for the second course. The origin of the toxic death observed at the fourth dosage level is difficult to determine: the initial symptoms and clinical history are concordant with severe allergic reaction and/or acute neurological toxicity, occurring in a debilitated patient dependent on hydrocortisone replacement therapy. Similar toxicity was not observed when the same dosages were given to children over 24 hours. However, the central nervous system toxicity of paclitaxel has already been reported: seizures in children (Hurwitz et al, 1993), alteration of consciousness (Webster et al, 1996; Chang et al, 1998; Glück et al, 1998) or neurovegetative disorders (Vassilomanolakis et al, 1998) in adults. The mechanism of acute neurological toxicity is not completely understood. The well known peripheral nervous system toxicity (Hurwitz et al, 1993; Cavaletti et al, 1995; Seidman et al, 1995; Glantz et al, 1996), also observed in our study, might reflect a direct axonal toxicity, that may also affect the central nervous system. However, brain penetration of paclitaxel is known to be limited (Eiseman et al, 1994; Glantz et al, 1995). Nevertheless, grade IV neurological toxicity was encountered for the highest plasma concentrations and AUC of paclitaxel and the lowest clearances. The role of ethanol, used as paclitaxel solvent, must also be stressed in the acute neurological toxicity. Ethanol causes cardiovascular and central nervous system toxicity, direct vasodilatation (Litovitz, 1986) and hypoglycaemia as well as metabolic acidosis (Ellenhorn, 1997). In our study, transitory metabolic acidosis but no hypoglycaemia was observed in both patients who experienced transitory coma at the end of the infusion; in one patient, a transitory increase of transaminases was observed (5 × N) but with no other hepatic abnormality. Ethanol is used as a solvent for other cytotoxic drugs such as etoposide or BCNU. The quantity of ethanol delivered with etoposide in a CARBOPEC regimen (Namouni et al, 1997) is 0.14 g kg^{-1} day^{-1} in 1 hour from D1 to D5. The quantity of ethanol delivered with BCNU in a BEAM regimen (Gaspard et al, 1988) is 0.3 g kg^{-1} in 1 hour. At 420 mg/m^2 dose level, the quantity of ethanol delivered with paclitaxel in this study was 1.05 g kg^{-1} in 3 hours. Lethal doses of ethanol in children are known to be around 3 g kg^{-1} but this is mainly reported after oral intoxication. Blood concentrations above 3 g l^{-1} are known to be potentially lethal. Ethanol assays in plasma samples collected for pharmacokinetic analysis showed elevated blood ethanol levels compatible with acute reversible neurological toxicity, but not necessarily explaining the toxic death (Moss, 1970; Sellers and Kalant, 1976; Landers, 1983; Adinoff et al, 1988). Somnolence and coma may be correlated partly with ethanol exposure (high C_{max} and duration of plasma alcohol concentrations above 0.5 g l^{-1}). Ethanol assays have also been reported in adults treated with paclitaxel. In one report (Webster et al, 1996), ethanol C_{max} after 175 mg/m^2 of paclitaxel did not exceed 0.09 g l^{-1} in 10 out of 12 patients, but reached values of 0.17 and 0.33 g l^{-1} in 2 other patients. Wilson (Wilson et al, 1997) reported a case of ethanol intoxication associated with a 3-hour dose of 350 mg/m^2 paclitaxel infusion, leading to an ethanol concentration of 0.98 g l^{-1}. Finally, the role of cremophor in acute neurological toxicity must also be discussed, as cremophor has been shown in vitro to induce demyelinization and axonal swelling and degeneration (Windenbank et al, 1994) at levels that are largely achieved in vivo using 3-hour paclitaxel infusions. In any case, in view of the acute neurological toxicity and elevated plasma alcohol concentrations which had not been anticipated and were not associated with any dose-limiting haematological toxicity, we considered that this paclitaxel schedule was definitely not recommended in children. Indeed, because of the suspected role of solvents in this non-haematological severe toxicity, the study was closed without including the 2 more patients at the third dose level.

The other main toxicity encountered in this study was allergic. Allergy to paclitaxel is usually thought to be due to cremophor and is generally successfully prevented by anti-allergic premedication. Cremophor has been implicated as a probable cause of anaphylactoid reactions following administration of cremophor-containing drugs, such as cyclosporin or teniposide (Chapuis et al, 1985; Magalini et al, 1986; MacLeod et al, 1991; Theis et al, 1995; Nolte et al, 1998). Such a severe allergic reaction might also be involved in the origin of the toxic death that occurred in our study. However, given the allergic toxicity described with the analogue docetaxel (Seibel et al, 1999), which is delivered without cremophor EL, paclitaxel itself might also be involved in these allergic reactions. The use of an H_2-blocking agent has been recommended before paclitaxel infusion in adults (Schiller et al, 1994), but remains controversial and was not used in the previous phase I trial in children (Hurwitz et al, 1993).

The pharmacokinetics of paclitaxel in 3 hour infusion showed specific characteristics. Clearance of paclitaxel appeared to decrease as the dosage increased from 240 to 420 mg/m^2 and the maximum concentration and area under the curve increased more than in proportion to the dose. As in adults (Eisenhauer et al, 1994; Sonnichsen et al, 1994a; Gianni et al, 1995; Kearns et al 1995), these results suggest that paclitaxel pharmacokinetics is non-linear when the drug is administered as a 3-hour infusion in children.

Mean paclitaxel clearances in children (8.48 to 2.74 l h^{-1}/m^2) were within the range reported for adults after short-term administration (Sonnichsen et al, 1994a; Gianni et al, 1995; Kearns et al, 1995) but clearances tended to be lower after the 3-hour infusion (our study) compared to the 24-hour infusion value in children (Sonnichsen et al, 1994b). However, although it has previously been proposed that paclitaxel's nonlinear pharmacokinetic behaviour is due to saturable distribution and elimination processes, recent reports strongly suggest that this non-linear behaviour results from entrapment of paclitaxel in cremophor EL micelles in plasma (Sparreboom et al, 1996b, 1999; Van Tellingen et al, 1999). This effect makes it difficult to use the clearance as parameter for drug exposure, as the actual exposure to 'free' paclitaxel depends on the plasma level of cremophor EL. The pharmacokinetics of cremophor EL itself was only studied in adults (Rischin et al, 1996; Sparreboom et al, 1999; Van Tellingen et al, 1999). These studies have shown that the C_{max} of cremophor EL increases linearly with the dose administered. At the highest dose level tested in adults (Sparreboom et al, 1999) of 225 mg/m^2, the C_{max} of cremophor EL was 6.58 ± 0.52 µl ml^{-1} (i.e. 6.94 0.55 mg ml^{-1}), which is comparable to the levels found in our study in children receiving the lowest dose of 240 mg/m^2. Further increments in the dose given to children resulted in a linear increase in the cremophor EL C_{max} levels. Consequently, the C_{max} level of cremophor EL at the highest dose (420 mg/m^2) is more than 2-fold higher than in adults receiving conventional doses of paclitaxel, which might explain the apparent non-linearity of paclitaxel's clearance and the low haematological toxicity.

Regarding anti-tumour activity, the only tumour response in this study was obtained in one patient treated for recurrent rhabdomyosarcoma. It might be interesting to investigate other paclitaxel schedules in this diagnosis (Hurwitz et al, 1993).

In conclusion, dose-limiting toxicity of this modality of paclitaxel administration in children, is neurological and, possibly, allergic. The combination of paclitaxel, ethanol and cremophor EL is responsible for neurotoxicity; since all components may play a role, it does not seem appropriate to relate toxicity to specifically one component. Paclitaxel administration as a 3-hour infusion every 3 weeks is definitely not recommended in children. Short-term infusions may be used for administration at lower doses, such as weekly (Glantz et al, 1996) or fractionated daily doses (Don Francesco et al, 1996). In addition, plasma alcohol levels should be monitored in children receiving paclitaxel at any dose level.

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