Anti-Cancer Drugs 2002, **13,** pp. 481–489

Clinical report

Pharmacodynamics of non-break weekly paclitaxel (Taxol) and pharmacokinetics of Cremophor-EL vehicle: results of a dose-escalation study

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We characterized the toxicity and determined the maximum tolerated dose of non-break weekly paclitaxel (Taxol) in chemotherapy-naive cancer patients, and studied pharmacokinetics of the formulation vehicle Cremophor-EL with this schedule. Twenty-three patients with primary refractory solid tumors received weekly paclitaxel at the dose range of 70–200 mg/m^2. As dose-limiting toxicity we defined granulocytopenia grade $\geqslant$2 causing a treatment delay for more than 2 weeks, or febrile neutropenia or grade >2 organ-specific toxicity. Plasma kinetics of Cremophor-EL were analyzed over the first five courses of treatment. Non-break weekly paclitaxel was feasible at doses up to 110 mg/m^2, while granulocytopenia precluded scheduled administration of doses $\geqslant$130 mg/m^2. Clinically relevant peripheral neurotoxicity tended to occur at around 1500 mg/m^2 cumulative dosage at weekly doses $\geqslant$110 mg/m^2. Detectable Cremophor-EL levels were found in all pre-dose samples, but there was no evidence of accumulation up to the sixth course. Our results, discussed in the light of an overview of published data, suggest that chronic weekly administration of paclitaxel is feasible and with a lack of significant accumulation of Cremophor-EL levels at doses up to 90 mg/m^2. [© 2002 Lippincott Williams & Wilkins.]

Key words: Cremophor-EL, paclitaxel, pharmacokinetics, Taxol, weekly administration.

Introduction

Paclitaxel (Taxol), the prototype of taxanes, is widely used today in the treatment of a variety of tumor types, typically administered as a 3-h i.v. infusion every 3 weeks.[1] However, the optimal schedule, infusion time and dosage of this antimitotic agent have not been defined. Weekly administration of brief infusions of paclitaxel is emerging as a novel therapeutic option of improved therapeutic index[2] and is also considered in remission maintenance therapeutic regimens (GOG Trial 175), for its mild toxicity and indications of anti-angiogenetic activity.[3,4]

We studied the pharmacodynamics and determined the maximum tolerated dose (MTD) of chronic non-break administration of weekly paclitaxel in chemotherapy naive cancer patients, and analyzed pharmacokinetics of its formulation vehicle Cremophor-EL with this schedule of administration. At completion of this trial further information on weekly paclitaxel was made available. However, this is the first phase I trial of chronic non-break weekly administration of paclitaxel to appear in the literature. It complements existing information and investigates the pharmacokinetics of the formulation vehicle Cremophor-EL with this schedule. We considered the pharmacokinetic study of Cremophor-EL to be of primary interest with weekly paclitaxel administration with regard to its low elimination rate, and potential biological and pharmacological activities.[5,6] The results of this study are discussed in the light of a review of already existing data in an attempt to integrate all the available information.

Patients and methods

Study design and objectives

This open-label, dose-finding and pharmacokinetic study was conducted at the Medical Oncology Department, University of Ioannina, Greece during

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the period 1996–1999. Written informed consent was obtained from all patients before study entry. Primary objectives were: (i) to characterize the toxicity profile of escalating doses of weekly paclitaxel administered by 1-h infusion, (ii) to determine the MTD, the dose-limiting toxicity (DLT) and the cumulative toxicity of chronic non-break weekly paclitaxel, and (iii) to investigate the pharmacokinetics of its vehicle (Cremophor-EL) at different dose levels with this schedule.

Formulation, administration and dose escalation

Paclitaxel was supplied as a commercially available 6 mg/ml concentrate, in 5 ml vials in polyoexythylated castor oil (Cremophor-EL) 50% and dehydrated alcohol, USP 50% vehicle. Final infusion was prepared before administration at a concentration of around 0.7 mg/ml by diluting an appropriate amount of concentrated paclitaxel solution with 0.9% sodium chloride in glass containers. Paclitaxel was administered as a 60-min infusion every week on a non-break basis.

Anti-allergic prophylaxis was given before each paclitaxel infusion. It consisted of 32 mg methylprednisolone given orally the day before, and 16 mg dexamethasone, 0.1 mg/kg dimetindene maleate and 100 mg ranitidine given i.v. 30 min prior to paclitaxel administration.

As a starting dose level we selected 70 mg/m^2, which is known to produce active plasma levels of paclitaxel.[7] Dose increments were planned in the order of 20 mg/m^2. Dose escalation followed the 3+3 cohort design. A minimum of three assessable patients (receiving treatment for at least 3 consecutive weeks) entered at non-toxic dose levels. In case of grade $\geqslant 2$ toxicity, except alopecia or inadequately treated nausea/vomiting, three more patients were treated at the same dose level. Intra-patient dose escalation was not applicable in this study and prophylactic use of granulocyte colony stimulating factor (G-CSF) was not allowed. Nothing else was infused through the line used to administer paclitaxel.

Patients

Patients enrolled in this study had to meet the following criteria. They had to be between 16 and 75 years old, in a relatively good physical condition with a PS <2 of the WHO scale and life expectancy >3 months, and to have adequate renal and normal liver function defined by serum creatinine <2 mg/ml and normal serum levels of bilirubin and transaminases. Upon entry into the study, absolute neutrophilic and platelet counts were to be >1500 and $>100\,000/\mu$l, respectively. No previous chemotherapy or concurrent biological therapy or immunotherapy was allowed in this trial. In cases of extended field irradiation, an interval of at least 6 weeks prior to initiation of treatment was required. Patients with CNS involvement, clinically relevant peripheral neuropathy and significant cardiac disease were considered ineligible for this study. All patients gave their informed consent prior to treatment initiation.

Monitoring

Patients were monitored before the start of treatment and weekly thereafter by physical examination, blood counts, serum biochemistry and urinalysis until 4 weeks post last administration of paclitaxel. In case of treatment discontinuation due to adverse events, or adverse events at the end of treatment possibly related to the study medication, toxicity had to be assessed until resolution of abnormality at intervals not exceeding 6 weeks. Patients had baseline CXR and ECG. Pre-treatment imaging studies for response assessment were done in all enrolled in the study patients and scheduled to be repeated every 6–8 weeks. In case of occurrence of neuropathy grade $\geqslant 2$, patients were referred for detailed neurological clinical and electrophysiological evaluation.

Safety and efficacy assessment

Toxicity was graded according to the NCIC-CTG expanded common toxicity criteria (revised 21 December 1994). Adverse events were recorded throughout the period of the clinical trial and until 4 weeks post last treatment administration. Any abnormal outcomes were documented as adverse events and their relationship to the study drug was characterized. As DLT, we defined granulocytopenia grade $\geqslant 2$ causing a treatment delay for >2 weeks, febrile neutropenia or grade >2 organ-specific toxicity. As MTD, we defined the highest dose that produced the DLT in at least two of six patients.

Although efficacy evaluation was not an end-point in this trial, tumors were assessed for response. We

used the WHO criteria which define as a complete response the disappearance of all known disease and as partial response an at least 50% decrease of the sum of the products of the largest perpendicular diameters of all measurable bidimensional lesions or the sum of largest diameters of all unidimensional lesions. Patients were considered evaluable for antitumor efficacy of treatment if disease measurements were recorded over at least a 6-week period from the first dosing of therapy. Objective responses needed to be confirmed with a second assessment not less than 4 weeks apart.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were obtained at the following time points: 0, 0.25, 0.5, 0.75, 1, 2, 3, 5 and 24 h post infusion, and on day 8, before the second and every following paclitaxel infusion up to the sixth consecutive weekly course. Blood samples (5 ml) were collected in heparinized tubes from an indwelling i.v. catheter set in the arm not used for the treatment infusion. They were immediately centrifuged at 2500 *g* for 10 min at 4°C and separated plasma was stored in polypropylene vials at −20°C.

The analytical work was performed at the Laboratory of Analytical Chemistry, European Environmental Research Institute, Ioannina, Greece. The reversed-phase high-performance liquid chromatographic (HPLC) assay used was developed by Alex Spareboom.[8] This assay is based on extracting and quantifying ricinoleic acid, which is the major component of Cremophor-EL, following saponification of Cremophor-EL in alcoholic KOH. Margaric acid (Sigma, St Louis, MO) was used as the internal standard. The derivatized compounds were separated at ambient temperature by a Shimadzu LC-10AD HPLC system equipped with a spectrophotometer detector M10A (Kyoto, Japan) by using an analytical column (250 × 4 mm) packed with 5 μm Spherisorb ODS-1. The mobile phase was a methanol: acetonitrile: 10 mM potassium phosphate buffer, pH 7.0 (72:13:15 v/v) and was delivered at a flow rate of 0.8 ml/min. Detection was executed by UV/Vis diode array absorption at 280 nm.The lower limit of detection was 0.01% v/v of Cremophor. Peak recording and integration was performed at a PC/HP Vectra 486/33 VL equipped with a LC Workstation class LC10 (Kyoto, Japan). Peak area ratios of ricinoleic acid to the internal standard versus concentrations of the standard were used for quantitative computations. Calibration standards were prepared by spiking drug-free human plasma at concentrations of 0.01, 0.025, 0.05, 0.1, 0.25, 0.5 and 1.0% v/v (μl/ml=10 × % v/v) of Cremophor-EL by serial dilutions of the 1.0% v/v standard solution. Quality control samples were prepared at three levels: 0.05, 0.1 and 0.5 v/v of Cremophor. Drug-free human plasma was obtained from the Blood Transfusion Unit of Ioannina University Hospital. The within-day and day-to-day coefficient of variance was <12% in this study, and the percentage deviation of the procedure over the validated concentration range of 0.01–1.0% (v/v) of Cremophor-EL in plasma was <8%.

Pharmacokinetic evaluations were based on the real blood sampling times as documented on the respective forms. Non-compartmental pharmacokinetic calculations were performed with the WinNonlin version 2.1 program (Pharsight, Palo Alto, CA). The area under concentration–time curve from time zero to infinity (AUC_{inf}) was computed by using the linear trapezoidal rule from time zero to time corresponding to last sampling point (C_{last}) and extrapolation to infinity, based on the last observed concentration. The total plasma clearance and terminal half-life ($t_{1/2\lambda z}$) were calculated using the equations: $Cl=dose/AUC_{INF}$ and $t_{1/2\lambda z}=\ln 2/lz$ [where lz is a first-order rate constant associated with the terminal (log-linear) portion of the curve, estimated via linear regression of time versus log concentration]. Time above plasma levels 1 μl/ml (0.1% v/v) and 1.35 μl/ml (0.135% v/v) that are considered as thresholds for exerting different pharmacological activities of Cremophor-EL[9,10] were calculated directly from the graph.

Pharmacokinetic parameters were analyzed by using the paired *t*-test and two-tailed *p* values for testing the differences between pharmacokinetic values obtained at the first and fifth course at different dose levels, and ANOVA for testing variability among the means of terminal $t_{1/2}$ values among the different dose levels. The computer program GraphPad Instat version 3.05 was used for calculations (San Diego, CA).

A computerized Internet PubMed search of English and non-English language medical literature was conducted by using Reference Manager version 9.5 for the period 1980 to April 2001. For the search we used as 'title' words, the words paclitaxel or Taxol or Cremophor-EL combined with each one of the weekly, pharmacokinetics or pharmacodynamics set as 'all-fields' words.

Results

Treatment administration

Twenty-three patients with a variety of cancer types and multiple metastases entered onto the study from June 1996 to June 1999. All patients, but one who had a relapsed primary CNS lymphoma, had not been given prior chemotherapy (Table 1). On average, 9.1 weekly courses of treatment (range 1–22) were given per patient. Eight patients received a minimum 10 non-break weekly courses of treatment. In five cases treatment was discontinued due to disease progression. Seven patients went off study because of DLT and 11 others decided to withdraw while in partial remission or stable disease. Those were all three patients treated at a dose level of 70 mg/m^2, four out of seven at 90 mg/m^2, all three at 110 mg/m^2 and one out of six at 130 mg/m^2. Although MTD, as defined in Methods, was reached at 130 mg/m^2, we further investigated dose levels of 150 and 200 mg/m^2 per week to check against published data that suggested feasibility of administering weekly doses paclitaxel over 200 mg/m^2.[11]

Table 1. Patient demographics

Patients entered	23
male	16
female	7
Age	
median	60
range	40–72
Performance status	
median	1
range	0–2
Naive patients	22
Prior chemotherapy	1
Primary sites	
cancer of unknown primary	8
lung (NSCLC)	6
sarcoma	3
mesothelioma	3
pancreatic	2
brain (non-Hodgkin's lymphoma)	1

Toxicity

The toxicity of weekly paclitaxel is profiled in Table 2. The MTD at this schedule was 130 mg/m^2/week. At this level, dose-limiting neutropenia occurred in three out of six patients. Two of them developed grade 3 and 4 neutropenia, respectively, that caused a >2-week treatment delay, while a third patient was hospitalized for febrile neutropenia grade 4. All toxic events occurred after the second weekly administration. A grade 3 neutropenia occurred at 90 mg/m^2 after the third weekly administration in a patient with cancer of unknown primary site and sarcoidosis. At 150 mg/m^2 one patient developed dose-limiting grade 4 neutropenia after two courses, and at 200 mg/m^2 both treated patients developed dose-limiting grade 4 neutropenia after the first and second course, respectively. At weekly doses of 110 mg/m^2 and lower hematological toxicity was clinically irrelevant and did not intervene with regular weekly administration of treatment.

Neurotoxicity, myalgia and alopecia were the most common non-hematological toxicities recorded in this trial. Peripheral neuropathy was a considerable toxic consequence of weekly paclitaxel. Minor (grade 1) neurotoxicity occurred at all studied dose levels, but clinically relevant grade 2 neurotoxicity developed progressively over a number of repeated drug administrations in patients treated with doses of 110 mg/m^2 and higher. This tended to become dose limiting at cumulative doses around 1500 mg/m^2 (1430–1650 mg/m^2) and lasted for a period of 1–6 months. Neuropathic symptoms were initially sensory, characterized by paresthesias and numbness in hands and feet, and progressed to experiencing difficulties in hand function and also proper walking in one patient treated at 110 mg/m^2 who received 1650 mg cumulative paclitaxel dose. Neurological

Table 2. Toxicity profile (worst grade toxicity per patient)

Treated patients	Dose level (mg/m^2/week)	Neutropenia			Neurotoxicity		Myalgia		Skin		Alopecia	
		2	3	4	1	2	1	2	1	2	1	2
3	70	1			1						2	
7	90		1		3			1		1	3	1
3	110				1	1	1			1	2	
6	130		2	2		2					3	2
2	150			1								1
2	200			2								

examination disclosed vibration and pin-prick sense abnormalities in these patients. Two cases of myalgia occurred at 110 mg/m^2 (grade 1) and 90 mg/m^2 (a distressing grade 2) after a minimum of four weekly doses but resolved soon after treatment discontinuation. No grade 3 myalgia was recorded. Eleven patients in all dose levels developed alopecia grade 1, and only three patients developed alopecia grade 2 at 90, 110 and 150 mg/m^2 after 10, 5 and 6 weeks of treatment, respectively.

Efficacy

Clinical responses, defined as sustained symptom relief and performance status improvement, were seen at all studied dose levels and partial response was documented in five cases. Those were two patients with cancer of unknown primary site, one with sarcoma, and one each with non-small cell lung cancer and mesothelioma, respectively, all treated at dose levels of 70–110 mg/m^2/week. The response duration lasted a median of 4 months (range 3–5).

Pharmacokinetics of Cremophor-EL

Blood sampling over the first five consecutive weekly courses of treatment was performed in seven consenting patients and in the other two at first administration only. They were two patients at each dose level of 70, 90 and 110 mg/m^2, and one patient treated at a dose level of 130 mg/m^2. One patient treated at 200 mg/m^2 was sampled only at first administration because he was taken off-study following the first course due to DLT. In another patient treated at 150 mg/m^2 pharmacokinetic analysis was considered not evaluable because of missing blood samples.

Pharmacokinetic parameters obtained at the first and fifth treatment course are listed in Table 3. There were no significant differences between pharmacokinetic values AUC_{inf}, C_{max}, C_{last} and plasma clearance, obtained at the first and fifth course at dose levels of 70–130 mg/m^2. The intra-occasion coefficient of variation over the first five consecutive courses was moderate: 24.6% (2–66%) for C_{max}, 20.5% (0–32.5%) for C_{last} and 8.95% (2.7–34%) for AUC_{inf}. Cremophor-EL plasma levels were constantly recorded over a minimum of 0.2 μl/ml in all cases. Levels higher than 1 μl/ml (0.1% v/v) which were shown *in vitro* to potentially reverse P-glycoprotein-associated multidrug resistance[9] were sustained for a

Table 3. Pharmacokinetic parameters of Cremophor-EL obtained at the first and fifth treatment courses (mean ± SD)

Paclitaxel dose (mg/m^2)	Cremophor-EL dose (mg/m^2)	AUC_{inf} (μl h/ml)			C_{max} (μl/ml)			C_{last} (μl/ml)			Cl (ml/h)		
		Course 1	Course 5	p^a	Cycle 1	Cycle 5	p^a	Cycle 1	Cycle 5	p^a	Cycle 1	Cycle 5	p^a
70	5.8	122.4 ± 41.5	149.4 ± 32.7		2.2 ± 1.4	2.6 ± 0.6		0.2 ± 0.07	0.2 ± 0.07		5.05 ± 17.1	40.6 ± 10.0	
90	7.5	186.5 ± 4.9	196.6 ± 20.3	NS	3.7 ± 0.0	3.7 ± 0.14	NS	0.3 ± 0.0	0.3 ± 0.07	NS	40.9 ± 0.0	38.3 ± 3.9	NS
110	9.2	337.5 ± 25.1	363.4 ± 19.3		5.6 ± 2.4	4.5 ± 1.6		0.7 ± 0.07	0.6 ± 0.2		25.0 ± 1.0	27.4 ± 1.7	
130	10.8	547.7	481.8		3.5	4.7		1.1	1.0		19.7	22.4	
150	16.6	591.5			10.5			1.3			281		

[a]Paired *t*-test of the differences between pharmacokinetic values obtained at the first and third/fifth courses at dose levels of 70—130 mg/m^2.

period of 2–20 h at a dose level of 70 mg/m^2, 14–65 h at a dose level of 90 mg/m^2 and continuously throughout the treatment period with doses higher than 130 mg/m^2. Concentrations higher than 1.35 μl/ml (0.135% v/v), which have been shown to antagonize paclitaxel cytotoxicity *in vitro*,[12] were recorded for 0–4 h at a dose of 70 mg/m^2, for 4–28 h at 90 mg/m^2, for 12–90 h at 110 mg/m^2, for over 48 h at 130 mg/m^2 and for over 160 h at 200 mg/m^2.

Interestingly, despite the residual Cremophor-EL levels recorded throughout the treatment period following the first course and thereafter, no significant accumulation for the first five courses was observed (p=0.1 for AUC_{inf}) at doses of 70–110 mg/m^2

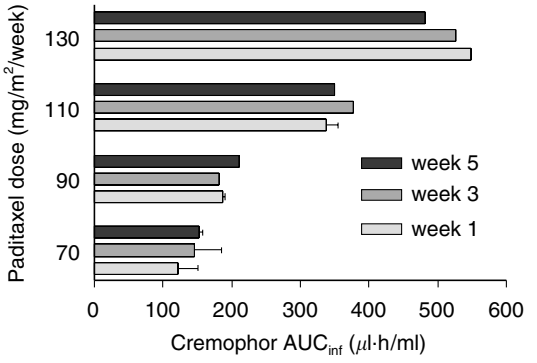

Figure 1. Cremophor-EL AUC_{inf} values of weeks 1–5, at dose levels 70–130 mg/m^2. Error bars represent SEM.

(Figure 1). The median observed volume of distribution (V_{ss}) was 3.59 × l/m^2 (±1.8 SD). Terminal half-life mean values at dose levels of 70–110 ranged between 70 and 77 h, but were significantly higher in two patients treated at 130 mg/m^2 ($t_{1/2}$= 183 h) and at 200 mg/m^2 ($t_{1/2}$=130 h) (Figure 2). A statistically significant difference with a trend towards a more prolonged terminal half-life at higher doses was detected by one-way analysis of variance (ANOVA, $p<0.0001$).

Discussion

Weekly paclitaxel is increasingly considered today in the treatment of cancer for three key reasons: minor hematologic toxicity, enhanced exposure of dividing cancer cells to this mitotic poison and exploitation of potential anti-angiogenetic activity.[2,3,13,14] Initial concerns for a possible compromise of anti-tumor activity with this schedule have not been verified and indications of efficacy are continuously expanding.[13,14] In addition, recent data show superior efficacy in terms of pathologic complete response for weekly paclitaxel as compared to conventional 3-weekly dosing in neoadjuvant setting for breast cancer.[15]

In our study chronic administration of weekly paclitaxel was found feasible at doses up to 90 mg/m^2. Granulocytopenia prevented scheduled

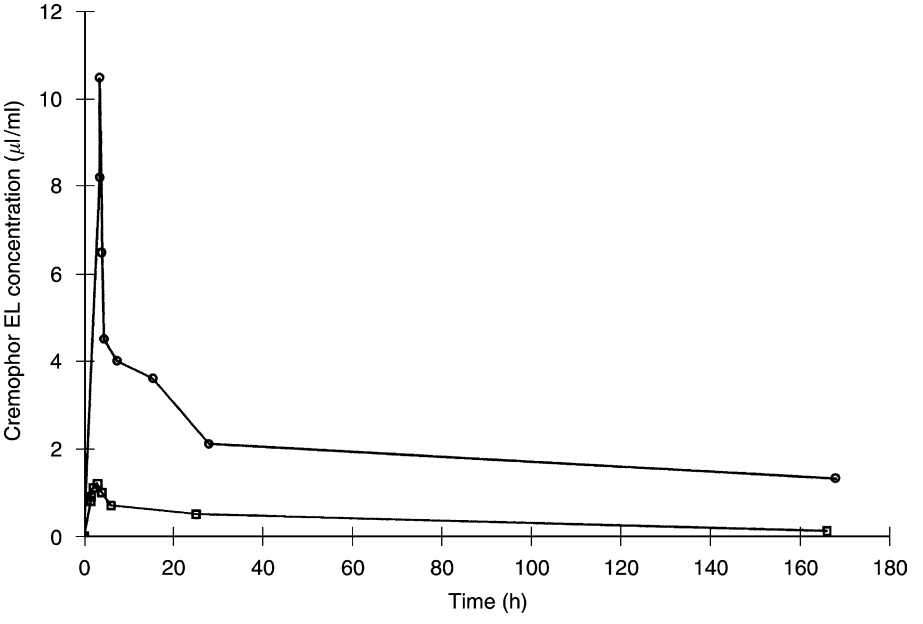

Figure 2. Plasma concentration versus time profile of Cremophor-EL in two patients treated with 1-h infusion of paclitaxel at dose levels of 70 (squares) and 200 (circles) mg/m^2, respectively.

treatment in half of the patients at 130 mg/m^2, and a clinically relevant peripheral neurotoxicity tended to occur at a cumulative dose around 1500 mg/m^2 with weekly doses of 110 mg/m^2 and higher. Neuropathy evolved gradually over repeated dosing to the point to intervening with everyday life activities in some patients. In line with our findings most published studies define the MTD of weekly paclitaxel around the dose of 100 mg/m^2 with an anticipated rest period of between 2 out of 6 and 3 out of 9 weeks (Table 4). Additionally, in a large phase II study conducted in breast cancer patients, peripheral neuropathy prohibited dose escalation above 100 mg/m^2 and the median delivered dose was 91 mg/m^2/week.[16]

However, the issue of maximum tolerated single doses of paclitaxel in dense dosing regimens (weekly or biweekly) remains debatable and there is good evidence that it is feasible to administer high doses of paclitaxel over a limited number of weekly cycles. Glanz reported safe administration of weekly paclitaxel at doses up to 250 mg/m^2 in patients with astrocytomas[11] and Akerley defined 175 mg/m^2 as the MTD of weekly paclitaxel in patients with advanced non-small cell lung cancer.[17] In both studies myelosuppression was minimal, but in the astrocytoma study treated patients were receiving anticonvulsants and high-dose corticosteroids, and in the other study only 83–50% of intended doses were actually delivered due to toxicity. Other investigators failed to administer 160 mg/m^2 paclitaxel every 2 weeks without G-CSF,[18] but interestingly the same dose administered on a weekly basis in elderly prostate cancer patients caused mostly grade 3 neurotoxicity and only minor myelotoxicity.[14]

We found that the nadir neutrophil counts with weekly paclitaxel occur following the second weekly drug administration. Interestingly, the lowest recorded absolute neutrophil counts at high[11,17] and also at moderate weekly doses[16] have consistently been recorded at the third week, increasing thereafter despite treatment continuation. These data indicate that bone marrow is possibly rendered resistant to subsequent paclitaxel doses through unknown mechanism. We can only speculate about the underling mechanism of this paradoxical phenomenon. The bone marrow sparing effect of repeated administration of high doses of paclitaxel may be related to paclitaxel itself or to the Cremophor-EL solvent which is co-administered at large quantities with paclitaxel, or it is possibly a combined effect of both agents. In the astrocytoma study the exceptional bone marrow tolerance of high weekly doses of paclitaxel was thought to be possibly

Table 4. Overview of dose-escalation studies with single agent paclitaxel on weekly administration schedules

Author	Patients	Tumor type	Prior chemotherapy	Dose range	Rest period (weeks)	MTD	Recommended dose (mg/m^2)	DLT (grade)	Objective response
Fennely[30]	18	ovarian	$\geqslant 2$	40–100	2–8 to 3–9	100	80	neutropenia (3)	13%
Loffler[31]	50	solid tumors	$\geqslant 2$	40–90	3–9		90	neutropenia (2)	40%
Klaassen[32]	20	solid tumors	$\geqslant 2$	70–100	2–8	100	90	neutropenia (4)	NR
Stumberg[33]	16	hepatocellular carcinoma	–	70–100	2–8	100	90	neutropenia (4)	modest
Akerley[17]	25	advanced non-small cell lung cancer	–	100–200	2–8	200	175	neutropenia (3)	56% RR
Glantz[11]	60	astrocytomas/ glioblastomas	–[a]	20–275	total six courses	250	225	neuropathy (3) neuropathy (3)	lacking

[a]With concurrent radiotherapy.

attributed to phenytoin, which may potentially alter the pharmacology of paclitaxel as an inducer of the P450 cytochrome enzyme system in the liver. However, no differences were detected between plasma kinetics of paclitaxel in those patients and historical data with the 3-weekly schedule.[11]

Liebmann *et al.* demonstrated a paradoxical survival of cells when incubated *in vitro* at high concentrations of paclitaxel, which are clinically achievable with brief infusions of conventional doses of paclitaxel.[19] They provided data crediting Cremophor-EL concentrations above 1.35 μl/ml for this phenomenon. We found that Cremophor-EL plasma levels may remain above this threshold in patients treated with weekly paclitaxel at doses 130 mg/m^2 and higher, over a period of days. At the lower studied dose levels we mostly found sustained Cremophor-EL plasma concentrations with the potential to reverse P-glycoprotein-associated multidrug resistance.[9] These and other data shape up a hypothesis that Cremophor-EL could play some role in the pharmacology of paclitaxel. There is evidence that Cremophor-EL may posses some pharmacological activity,[20–22] but its exceptionally prolonged plasma circulation time rebuts an active role in tumor sites and to the bone marrow.[23] Furthermore, Cremophor-EL solvent may also exert an indirect biological effect by causing disproportional accumulation of paclitaxel in plasma at short infusion schedules.[24] This is not the case for ethanol, the other major pharmacological formulation vehicle of paclitaxel, for which there is no data suggesting an active pharmacological role in the paclitaxel formulation.[25] Finally, paclitaxel may be inactivated at high concentrations through a mechanism of autoinduced metabolism[26] or the orphan nuclear receptor SXR,[27] which raises some scepticism about anticancer efficacy of high doses of the drug at dense dosing schedules. Convincing data do not exist, but less than expected antitumor activity has been observed for high doses of paclitaxel when administered as brief infusions either conventionally every 3 weeks[28,29] or at dense dosing schedules.[11]

Conclusion

In conclusion, we suggest that chronic administration of weekly paclitaxel is feasible at doses up to 90 mg/m^2. At this dosage weekly paclitaxel produces a low toxic chemotherapy with a lack of significant accumulation of Cremophor-EL. Due to the favorable toxicity profile it appears as a reasonable therapeutic option for cancer patients with a poor performance status or when considering therapeutic strategies of prolonged administration of paclitaxel. Clinical testing of weekly paclitaxel is warranted at this dosage against conventional 3-weekly regimens.

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(Received 22 October 2001; accepted 29 January 2002)