Comparative neurotoxicity of weekly non-break paclitaxel infusions over 1 versus 3 h

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We evaluated the effects of weekly short infusions of paclitaxel (PAC) on the development of a peripheral neuropathy (PNP) as primary endpoint. Patients with advanced cancer were randomized to a weekly regimen of PAC (100 mg/m^2) infused over 1 versus 3 h. PNP was evaluated by a clinical score including sensory symptoms, strength, tendon reflexes and vibratory sense (range 0–12; PNP >3 points). Kaplan–Meier-type curves were calculated. In total, 22 study centers enrolled 121 patients, 92 assessable for analysis. The probability to exceed a PNP score of 3 increased from 0.20 versus 0.30 after six to 0.68 versus 0.47 after 12 administrations (1 versus 3 h: $p = 0.66$). After 12 weeks of therapy only a quarter of assessable patients were free of PNP. Cox analysis yielded a relative risk of 1.10 for 1-h infusions ($p = 0.80$). We observed a rapid increasing risk of PNP manifestation in the course of weekly PAC administrations without significant differences between 1- and 3-h infusions. This is in contrast to pharmacokinetic observations indicating that a shortening of infusion time might enhance neurotoxicity by increasing the AUC of Cremophor. A majority of patients experiencing neurotoxic effects require the investigation of potential nerve protectors in future clinical trials accompanying PAC therapy. *Anti-Cancer Drugs* 14: 785–792 © 2003 Lippincott Williams & Wilkins.

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Introduction

Paclitaxel (PAC) dosing and scheduling have been evaluated in numerous clinical studies during the last 15 years, resulting in both a reduction of infusion times and an increase of dose density [1–8]. The establishment of a premedication with steroids and H_1/H_2 histamine blockers has led to a consequent reduction of infusion time from days to short-time infusions over 1 or 3 h [9]. The incidence of severe hematological toxicities could also be decreased by shortening infusion duration [6]. However, attempts to reduce the infusion time under the barrier of 1 h have led to a significant increase of anaphylactic reactions in nearly all patients [10]. As the application of growth factors can reduce the incidence and duration of therapy-induced leukopenias, neurotoxicity has meanwhile emerged as the remaining dose-limiting toxicity [11]. PAC is known to induce acute demyelination and chronic loss of axoplasmatic transport by affecting both Schwann cells and axons [12]. Predominantly sensory neuropathy has been described as dose-related toxicity of PAC [13–17]. Although several studies have confirmed the efficacy and safety of weekly short infusions with PAC as a single agent or in combination regimens, to our knowledge no prospective randomized investigation has examined the influence of infusion time (1 or 3 h) on the development of clinically significant PNP [18–21]. Therefore, we have performed an open, multicenter and randomized trial comparing weekly 1- and 3-h PAC infusions of 100 mg/m^2 with neurotoxicity as primary endpoint. Preliminary results of a subgroup analysis of this trial in 28 patients who underwent additional pharmacokinetic examinations showed comparable overall neurotoxicity [22].

Patients and methods

Eligibility criteria

Patients aged 18–75 years with histologically proven, locally advanced or metastatic cancer for whom PAC as monotherapy was a therapeutic option were candidates for this study. Patients with ECOG performance status >2, life expectancy <3 months, pre-existing peripheral neuropathy (PNP score prior to therapy >3) (Table 1), significant heart disease, known anaphylaxis against Cremophor (CrEL), chemo- or radiotherapy in the last 4 weeks, chemotherapy with taxanes in the last year, simultaneous anticancer treatment with hormone or

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immunotherapy, significant renal (serum creatinine $> 1.5 \times$ upper limit of normal), hepatic (total serum bilirubin $> 1.5 \times$ upper limit of normal) or hematological insufficiency (absolute neutrophil count $< 1.5 \times 10^9$/l and platelet count $< 75 \times 10^9$/l) as well as patients with bidimensionally non-measurable tumor were not included. In fertile women a negative test for pregnancy was required. While being in study, the participation in other trials was not allowed. All patients gave informed consent according to the local ethics committee requirements, and were monitored and treated at the participating center.

Study design

It was the primary aim of this trial to analyze the effects of weekly PAC short infusions with a dose of 100 mg/m^2 on cumulative PNP as endpoint, which was to be evaluated by the use of a clinical scoring system (Table 1) prior to, and after 6 and 12 weeks of therapy. The suggestion was made that 1-h infusions could lead to more PNP as compared to 3-h infusions. Additional analyses on secondary endpoints including general toxicity, response, survival and quality of life (QoL) were planned. Patients were to be randomized to two groups with different infusion times (1 versus 3 h). Based on a delayed recruitment after 1 year and the experience with the pharmacokinetic subgroup analysis in 28 patients [22] where less than expected patients were able to complete 12 weeks of therapy, we adapted the target number of patients to be enrolled from 210 to 120 estimating a failure quote of 30% each and decided to replace the primary planned simple comparison of frequencies of PNP events after 12 PAC administrations by the performance of a time-dependent analysis calculating the risk to develop a PNP in the course of therapy. An amendment was written and passed the Department of Ethics with a positive vote.

Randomization procedure

Having identified an eligible patient the study investigator of the treating center transmitted a completed eligibility checklist by facsimile to the study headquarters at the University Medical Center of Freiburg. Eligible patients were assigned a serial number and allocated to a weekly regime of PAC (100 mg/m^2) infused over 1 or 3 h by reference to a randomization list created by the Department of Biostatistics of Bristol-Myers Squibb, Germany.

Patients and participants

Between March 1999 and January 2002 a total of 121 patients had been enrolled by 22 German institutions partially recruited by Bristol-Myers Squibb to participate in this study. The majority of patients was enrolled by the University Medical Center of Freiburg ($N = 60$), the Tumor Biology Center of Freiburg ($N = 21$) and the Johanniter General Hospital in Duisburg ($N = 10$). A complete list of participating institutions and investigators is listed in Table 2. A subgroup of patients at the Tumor Biology Center of Freiburg and the University Medical Center of Freiburg participated after providing informed consent in additional pharmacokinetic analyses of PAC and CrEL. The specific methodologies and results of these pharmacokinetic analyses have been reported in individual publications [23,24].

Treatment plan

All patients were scheduled to receive a total of six weekly infusions of PAC (100 mg/m^2). After 6 weeks of therapy (defined as one cycle), response was evaluated bidimensionally, usually by computed tomography, according to the WHO criteria. Patients with a stable disease (SD), partial response (PR) or complete response (CR) after one cycle received a second cycle administered continuously without break, provided toxic effects were not prohibitive. After a maximum therapy duration of two cycles, response was re-evaluated and patients were off protocol therapy.

Toxicity assessment

Clinical examination, hematological diagnostics with a complete blood cell count as well as the assessment of symptoms and toxicity had to be performed weekly while patients were on therapy. Prior to therapy, after one and after two cycles these examinations had to be supplemented by the evaluation of the PNP score ranging from 0 (best) to 12 (worst) (Table 1), clinical chemistries (serum creatinine, AST, ALT, alkaline phosphatase and bilirubin), ECG analysis and performance status. With regard to patient safety, we decided in the early period of

Table 1 PNP score (modified after [14,17])

	Score			
	0	1	2	3
Sensory symptoms	none	numbness/paraesthesia in the feet	numbness/paraesthesia in feet and fingers	functionally disabling numbness/paraesthesia
Vibratory sense (tuning fork test)	8/8	<6/8	<4/8	none
Strength	normal	weak toe extension	weak toe extension and weak finger abduction	general/diffuse weakness
Tendon reflexes	normal	single reflexes reduced	single reflexes absent	all reflexes absent

Graduation of absolute PNP score: 1–3: mild PNP, 4–6: moderate PNP, >6: severe PNP.

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Table 2 Participating institutions and investigators in order of study entrance

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Practice for Obstetrics and Gynecology, Berlin, Germany	P. Klare
Tumor Biology Center, Freiburg i. Br., Germany	C. Unger K. Mross
Practice for Hematology and Oncology, Villingen-Schwenningen, Germany	E. Noah
Practice for Hematology and Oncology, Harrislee, Germany	W. Grimm
Department of Hematology and Oncology, Städtisches Klinikum, General Hospital, Karlsruhe, Germany	C. Ploeger
Practice for Hematology and Oncology, Freiburg i. Br., Germany	T. Reiber
Helios Rosmann Klinik, General Hospital, Breisach, Germany	B. Walter
Practice for Hematology and Oncology, Saarbruecken, Germany	J. Schimke G. Jacobs
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Department of Obstetrics and Gynecology, St Josefs Hospital, General Hospital, Wiesbaden, Germany	G. Hoffmann
Marienstift, Oncological Hospital, Schwarzenberg, Germany	A. Kohlstedt

the study to extend the protocol and to demand weekly evaluations of the PNP score in order to ensure optimal monitoring for neurotoxicity. An amendment was written and passed by the Department of Ethics with a positive vote. Hematological requirements for PAC administration were an absolute neutrophil count $\geq 1.5 \times 10^9$/l and platelet count $\geq 75 \times 10^9$/l. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (CTC) guidelines. In leukopenia grade 4 and/or febrile neutropenia as well as thrombocytopenia grade 4, a dose reduction of 25% for all further administrations was demanded. If the absolute neutrophil count was not available, it was calculated from the leukocyte count estimating a part of 55% granulocytes. Patients with an increase of their PNP score to 4–6 received a dose reduction of 25% for all further administrations, while those exceeding 6 were excluded. Dose reductions and removal of patients due to PNP were performed exclusively in accordance with the obtained score. In grade ≥ 3 cases of neuralgia, myalgia, arthralgia, nausea, vomiting, fatigue, vertigo, cephalgia, dysphagia, anorexia, obstipation or diarrhea it remained the decision of the local investigator to remove the patient from the study or to continue therapy; dose reductions were not allowed. Patients experiencing other non-hematological grade ≥ 3 toxicities had to be removed from the study. Grade 4 anaphylactic reactions were defined as significant hypersensitivity reactions (HSRs) with one or more of the following: generalized urticaria, respiratory distress requiring bronchodilatators, hypotension requiring pressure therapy or angioedema. Patients requiring a treatment delay of more than 14 days had to be removed from the study, always being able to receive further PAC administrations off study.

Drug administration

Vials containing 30 mg of PAC formulated in a mixture of CrEL and ethanol USP (1 : 1, v/v) were purchased from Bristol-Myers Squibb (Munich, Germany). PAC was diluted in 500 ml of 5% (w/v) dextrose in water and given to the patient via a peripheral or central venous catheter using a motor-driven programmable infusion pump over 1 or 3 h. Premedication consisted of 8 mg dexamethasone (the Tumor Biology Center of Freiburg used 20 mg dexamethasone according to their own premedication standard), an H_1 histamine blocker (2 mg clemastine or equivalent) and an H_2 histamine blocker (300 mg cimetidine or equivalent), all administered i.v. 30 min before PAC infusion.

Statistical calculations

For the statistical evaluation of the impact of PAC administration on the development of a PNP, we had to consider the dose dependency, which was well reflected by the number of weeks of therapies provided that dose reductions due to other reasons than PNP could be neglected. Using weeks of therapy as the timescale, we performed Kaplan–Meier-type analyses corresponding to the event in time when the PNP score exceeded 3 for the first time [25]. The choice of this cut-off point defining a clinically significant PNP is based on the graduation of the absolute PNP score (Table 1) and the inclusion criteria of this trial, as well. The effect of treatment delivery on the occurrence probability of the development of a PNP score > 3 was evaluated with a Cox regression model including the covariates patients age, gender and preceding therapies [26]. The results of this Cox regression model included estimated relative risks with 95% confidence intervals and p values for each risk

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factor. A final power calculation corresponding to the log-rank test for Kaplan–Meier estimated probabilities was performed.

Results

The characteristics of the 121 randomized patients are displayed in Table 3. Overall, 29 patients had to be excluded from the trial and 92 were assessable for a final analysis. Twelve patients with treatment pauses exceeding 14 days and a minimum of 6 completed weeks of therapy remained eligible for analysis of the first cycle, as well as two patients having refused further therapy after the first completed cycle and four patients with incorrect or missing dose reductions within the second cycle. The mean of delivered weeks, the number of dose reductions and the reasons for terminating the study are displayed in Table 4. Altogether, 114 of 121 randomized patients were eligible for an additionally performed intention to treat (ITT) analysis. The excluded patients could not be considered as documentation was completely missing ($N = 4$) or patients obtained no infusion with PAC at all ($N = 3$).

Table 3 Patient characteristics at baseline ($N = 121$)

Characteristic	1-h infusion		3-h infusion	
	N	%	*N*	%
No. of patients enrolled	60	50	61	50
No. of patients excluded, due to	11	9	18	15
refusal of therapy and/or withdrawal of consent	2	2	2	2
major study violations[a]	7	6	13	11
missing or insufficient documentation	2	2	3	2
Male/female	33/27		27/34	
Age (years)				
mean	59		58	
range	34–73		38–75	
Performance status (ECOG)				
0	16	13	10	8
1	26	21	32	26
2	8	7	10	8
≤ 2	10	8	9	7
Site of primary tumor				
breast	16	13	19	16
lung	19	16	17	14
ovary	1	1	3	2
bladder or ureter	5	4	2	2
esophagus	5	4	8	7
head/neck	6	5	7	6
CUP (cancer of unknown primary)	3	2	3	2
other (kidney, penis, anal, skin, thyroid gland, uterus)	5	4	2	2
Prior therapy	54	45	56	46
chemotherapy containing vinca	19	16	22	18
chemotherapy containing platinum	33	27	31	26
radiation therapy	31	26	29	24
PNP score prior to therapy				
median	1		1	
range	0–3		0–3	

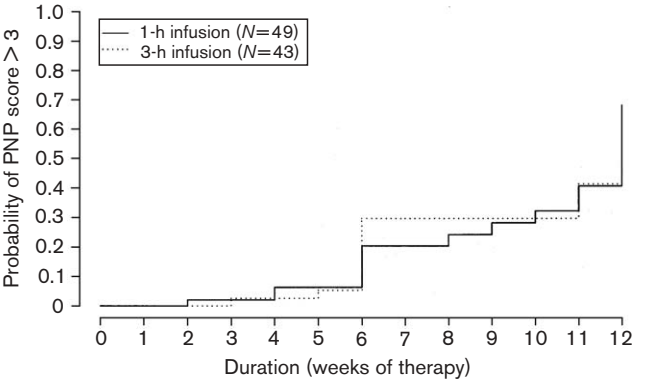
[a]Defined as any deviation from the scheduled infusion time ($N=2$), missing or incorrect dose reductions ($N=4$), start of therapy before randomization ($N=1$), therapeutic radiation while being on study ($N=2$), any evidence of primary ineligibility after study entrance ($N=4$), missing monitoring for toxicity or response ($N=3$), or treatment interruptions longer than 14 days ($N=4$).

Peripheral neuropathy

Overall, 92 patients were eligible for evaluation of PNP score. The comparison of treatment groups with respect to the probability of developing a PNP score > 3 showed similarly increasing curves during the observation period (Fig. 1). After the first cycle 82% (1-h) versus 81% (3-h) and after the second cycle 27% (1-h) versus 23% (3-h) of the patients neither showed a significant PNP nor had been censored yet. The estimated probability to exceed PNP score 3 after one cycle was 0.20 (95% CI = [0.11;0.36]) for 1- and 0.30 (95% CI = [0.18; 0.47]) for 3-h infusions. After 12 weeks of therapy this probability increased to 0.68 (95% CI = [0.49; 0.85]) for 1- and to 0.47 (95% CI = [0.29; 0.69]) for 3-h infusions. Applying the log-rank test, this difference between the two infusion groups was not significant ($p = 0.66$). Using the Cox regression model the estimated relative risk of PNP score > 3 was nearly equal for 1- and 3-h infusions (Table 5). Similar results were calculated for the effects of age, gender and prior radiation. For prior therapies containing vinca or platinum as typical agents well known to induce peripheral neuropathies, we found only for platinum an increase of risk for PNP score > 3 (factor 1.43) in the course of therapy with PAC, which was not significant (Table 5). Comparable results were obtained for the additionally performed ITT analysis (Fig. 2). Using the log-rank test the observed difference was found not to be significant ($p = 0.22$). In the Cox regression analysis the risk to PNP score > 3 was slightly, but also not significantly increased for 1-h infusions (factor 1.47) as well as for preceding therapies containing platinum (factor 1.24) (Table 5).

Considering the sample size $N = 92$ of this study a *post-hoc power calculation* corresponding to the log-rank test was performed. Basing on the Kaplan–Meier estimated probabilities to exceed PNP score 3 after 12 weeks of

Fig. 1



Kaplan–Meier-type analysis of development of clinically significant PNP (score > 3) in course of therapy in patients assessable for toxicity ($N=92$).

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therapy we assumed a 31% reduction of this probability for 3- as compared to 1-h infusions. Considering the study specific parameters the power to detect a 31% reduction would be 54%, while the power to detect a 50% reduction would be 89% (Fig. 3).

General toxicity

Toxicity data were available for 92 patients. General toxicity assessment was performed according to the National Cancer Institute CTC (Table 6). Grade 3 or 4 leukopenias were reported in five patients of the 1- and in four patients of the 3-h infusion group (10% each). One extensively pretreated patient died from grade 4 febrile neutropenia after the first administration of PAC in the 1-h group. In another patient with 3-h infusions, grade 3 febrile neutropenia occurred at week 4 leading to hospitalization and treatment stop, and in one further case with 1-h infusions, febrile neutropenia grade 3 at week 2 was reported after implantation of an esophageal stent. This patient was able to continue chemotherapy after sufficient leukocyte regeneration and antibiotic therapy; a dose reduction was not performed based on the local investigator's decision. No thrombocytopenia grade >1 was observed. Grade 3 anemia occurred in five patients (5%). Altogether, incidence and extent of hematological toxicities were comparable in both infusion groups. One grade 3 infection without neutropenia was observed (1%).

Severe HSR occurred in three patients (3%) exclusively in the 3-h group, requiring cardiopulmonary resuscitation in one case. All these patients received a dose of 8 mg dexamethasone as premedication. One patient was removed from the 1-h group due to rapidly developing grade 3 heart failure (1%).

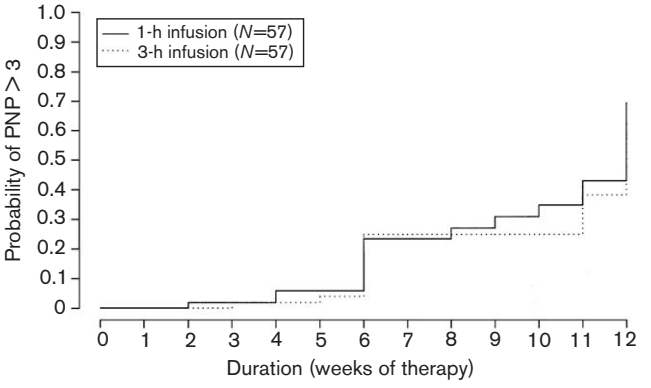
A number of grade 3 or 4 neurological side-effects other than neuropathy have been reported, including cephalgia (2%), arthralgia (4%), myalgia (4%), neuralgia (5%), vertigo (3%), hearing (1%) and visual disturbance (2%). A single case of grade 4 visual toxicity was described for the 3-h infusion group (1%). In total, two patients with visual disturbances within and after PAC infusion had to be removed from both study groups. All patients with pain documented as toxicity ($N=24$) were re-evaluated. Seven of them were found not to be assessable for

Table 4 **Treatment delivery ($N=92$)**

	1-h infusion	3-h infusion
Patients	49	43
Total assessable weeks of therapy	370	320
mean	7.6	7.4
SD	3.1	3.5
Dose reductions of 25% in assessable weeks		
due to PNP (score: 4–6)	10	9
due to other toxicities than PNP	0	0
Performed at mean week of therapy	7.8	7.7
Reasons for termination of study		
completed	13	14
disease related deaths	3	1
progressive diseases	13	11
PNP score >6	3	0
grade 3 or 4 toxicities[a] (not PNP)	6	5
reported severe adverse events	2/6	5/5
Excluded after one completed cycle, due to		
treatment pauses >14 days	7	5
incorrect or missing dose reductions	2	2
refusal of further therapy	0	2
investigators decision, other reasons[b]	2	3

[a]Significant thoracic or abdominal pain during PAC infusion ($N=3$), severe HSRs ($N=3$), acute visual disorders ($N=2$), neutropenic fever ($N=2$) or acute heart failure ($N=1$).
[b]General intolerance ($N=1$), performance status (ECOG >2) ($N=1$), indication for radiation therapy ($N=2$) or progredient acral paresthesias ($N=1$).

Fig. 2



Kaplan–Meier type analysis of development of clinically significant PNP (score >3) in course of therapy in patients assessable for ITT ($N=114$).

Table 5 **Cox regression analysis**

Effect on PNP score >3	Patients assessable for toxicity ($N=92$)			Patients assessable for ITT ($N=113$[a])		
	relative risk	95% CI	*p*	relative risk	95% CI	*p*
1-h infusions	1.10	[0.52;2.35]	0.80	1.47	[0.73;2.93]	0.28
Age	1.02	[0.98;1.07]	0.39	1.00	[0.96;1.04]	0.92
Female gender	0.92	[0.43;1.96]	0.83	1.13	[0.55;2.32]	0.73
Prior radiation	0.96	[0.47;1.99]	0.92	0.81	[0.41;1.59]	0.54
Preceding chemotherapy containing vinca	0.70	[0.30;1.65]	0.42	1.01	[0.48;2.15]	0.97
Preceding chemotherapy containing platinum	1.43	[0.65;3.14]	0.37	1.24	[0.59;2.62]	0.57

[a]For one patient one auxiliary factor of the ITT group ($N=114$) was not available.

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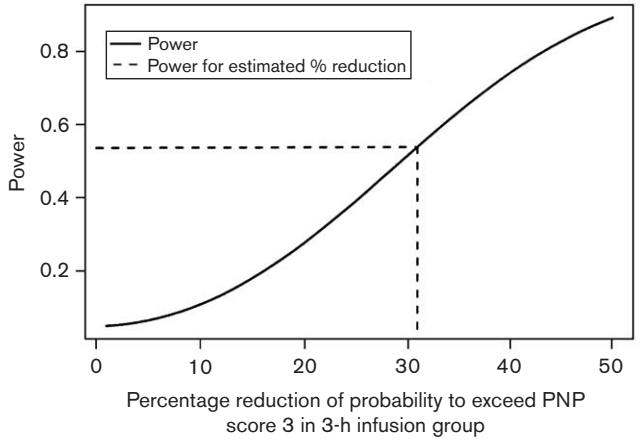
neuralgia as treatment-related toxicity any more as the complaints were obviously induced by the tumor or metastases ($N = 4$), pre-existing affections of the spinal column ($N = 1$), cardiopulmonary resuscitation ($N = 1$) or would better have been classified as myalgia ($N = 1$). All remaining patients with reported grade 3 neuralgia ($N = 5$) were treated with 1-h infusions; three of them had to be excluded from further therapy due to the investigator's decision. Altogether, grade 3 neurological toxicities including arthralgia, myalgia or neuralgia were predominantly observed in the 1-h infusion group at a mean therapy duration of 2 weeks (22 versus 5%). Three patients developed grade 3 fatigue (3%), one of them had to be excluded according to the investigator's decision. In two patients with tumors of the esophagus or head and neck, severe and probably not treatment-induced grade 4 dysphagia was reported (2%). One case of grade 3 skin toxicity with development of hand and foot syndrome was described at week 12. Other grade ≥ 3 non-hematological toxicities were quite uncommon and occurred in not more than 1% of all patients assessable for toxicity (Table 6).

Fig. 3



Power calculation corresponding to the log-rank test for Kaplan–Meier estimated probabilities to exceed PNP score 3 after 12 weeks of therapy depending on the unknown reduction of this probability in 3- as compared to 1-h infusions: $\alpha = 0.05$, N(1-h) = 49, N(3-h) = 43, non-compliance(1-h) = 0.59, non-compliance(3-h) = 0.67, probability of PNP > 3 (1-h) = 0.68 and (3-h) = 0.47.

Response, survival and QoL

Efficacy of therapy and QoL have been further secondary endpoints of the present trial. With respect to the heterogeneity of enclosed tumor types, the performed analyses on response and survival showed no significant differences between 1- and 3-h infusions (data not shown). The interpretation of the QoL data provided by the five-item Spitzer questionnaire was severely

Table 6 Highest degree of treatment-related toxicity ($N = 92$)

	1-h infusion (N=49)												3-h infusion (N=43)											
	Grade 1			Grade 2			Grade 3			Grade 4			Grade 1			Grade 2			Grade 3			Grade 4		
	N	%	*W*	*N*	%	*W*	*N*	%	*W*	*N*	%	*W*	*N*	%	*W*	*N*	%	*W*	*N*	%	*W*	*N*	%	*W*
Leukopenia	7	14	2.0	10	20	3.3	4	8	3.3	1	2	1.0	8	19	3.6	9	21	2.7	3	7	2.7	1	2	4.0
Thrombocytopenia	4	8	3.3	0	0	–	0	0	–	0	0	–	2	5	1.0	0	0	–	0	0	–	0	0	–
Anemia	21	43	1.7	14	29	3.8	3	6	5.3	0	0	–	16	37	5.9	10	23	2.9	2	5	2.0	0	0	–
Febrile neutropenia	–	–	–	–	–	–	1	2	2.0	1	2	1.0	–	–	–	–	–	–	1	2	4.0	0	0	–
Infection, non-neutropenic	0	0	–	5	12	4.6	0	0	–	0	0	–	3	7	6.3	3	7	4.0	1	2	7.0	0	0	–
Allergy/anaphylaxis	1	2	3.5	1	2	3.0	2	4	2.0	0	0	–	2	5	1.0	1	2	10.0	0	0	–	3	7	3.3
Cephalgia	6	12	2.2	3	6	4.7	2	4	6.0	0	0	–	7	16	4.6	1	2	5.0	0	0	–	0	0	–
Arthralgia	4	8	3.3	5	10	4.6	3	6	2.7	0	0	–	5	12	4.4	2	5	5.0	1	2	1.0	0	0	–
Myalgia	7	14	2.9	3	6	1.0	3	6	4.0	0	0	–	4	9	2.0	6	14	2.5	1	2	1.0	0	0	–
Neuralgia	5	10	4.6	2	6	6.0	5	10	2.4	0	0	–	2	5	7.0	2	5	1.0	0	0	–	0	0	–
Vertigo	3	6	3.3	2	4	4.0	1	2	5.0	0	0	–	4	9	3.5	1	2	2.0	2	5	4.0	0	0	–
Hearing disturbance	2	4	3.0	6	12	4.0	1	2	6.0	0	0	–	2	5	5.5	2	5	2.5	0	0	–	0	0	–
Visual disturbance	2	4	5.0	1	2	2.0	2	4	8.0	0	0	–	3	7	9.3	0	0	–	0	0	–	1	2	3.0
Cardiac toxicity[a]	0	0	–	2	4	4.0	1	2	7.0	0	0	–	1	2	1.0	0	0	–	0	0	–	0	0	–
Alopecia	13	27	3.7	24	49	4.6	0	0	–	–	–	–	9	21	4.3	24	56	4.4	0	0	–	0	0	–
Fatigue	4	8	1.0	4	8	4.8	1	2	6.0	–	–	–	2	5	1.0	5	12	2.2	2	5	8.0	0	0	–
Dysphagia	6	12	1.3	0	0	–	0	0	–	1	2	4.0	2	5	2.5	0	0	–	0	0	–	1	2	6.0
Anorexia	15	31	3.6	3	6	2.3	0	0	–	0	0	–	10	23	4.4	2	5	1.0	0	0	–	0	0	–
Nausea	12	24	2.3	4	8	2.8	1	2	10.0	–	–	–	7	16	1.4	5	12	4.2	0	0	–	–	–	–
Vomiting	7	14	2.3	3	6	3.0	0	0	–	0	0	–	4	9	1.5	3	7	4.0	0	0	–	0	0	–
Stomatitis/pharyngitis	10	20	2.8	2	4	5.5	0	0	–	0	0	–	7	16	4.9	4	9	4.3	0	0	–	0	0	–
Diarrhea	7	14	3.3	2	4	5.5	0	0	–	0	0	–	3	7	6.7	3	7	4.3	1	2	3.0	0	0	–
Obstipation	6	12	1.2	4	8	2.8	1	2	5.0	0	0	–	5	12	2.4	2	5	1.0	0	0	–	0	0	–
Nail/skin disorders	3	6	5.3	2	4	2.5	0	0	–	0	0	–	2	5	7.0	3	7	4.7	1	2	12.0	0	0	–
Pruritus	2	4	3.5	1	2	2.0	0	0	–	–	–	–	2	5	9.0	1	2	6.0	0	0	–	0	0	–
Edema	4	8	5.3	1	2	3.0	0	0	–	0	0	–	3	7	2.3	3	7	5.7	0	0	–	0	0	–

Toxicity was assessed weekly according to the National Cancer Institute CTC. Obtained CTC toxicities for sensory and motor neuropathy are not displayed in this table as PNP was primarily monitored by PNP score. Thus, dose reductions and removal of patients due to PNP were performed exclusively in accordance with the PNP score. N = number of patients experiencing a maximum grade of toxicity; W = mean week of first appearance of this maximum grade.

[a]Cardiac toxicity including angina pectoris, arrhythmias and one case of grade 3 heart failure.

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limited by the poor compliance with this part of our trial and is therefore not demonstrated.

Discussion

In our analysis, neurotoxicity was primarily obtained by an easily applicable clinical scoring system to ensure the comparability of results [14,17]. Regarding the development of PNP, we could show that the risk of developing a clinically significant PNP increases with therapy duration. After 6 weeks of therapy, about 80% and after 12 weeks, only about 25% of our patients showed neither a significant PNP nor had been censored. As all patients received a dosage of 100 mg/m^2 and as no dose reductions due to reasons other than PNP had to be performed, the number of weeks of therapy also reflects the cumulative dosage in those patients having PNP score > 3 the first time. Thus, we conclude that it is mainly a question of cumulative dosage until each patient develops a clinically significant PNP. In a recently published dose-escalation study, the authors observed a clinically relevant PNP at around 1500 mg/m^2 cumulative dose of PAC [27]. Due to these cumulative effects it is necessary to ensure close monitoring of PNP. We noted a slight trend towards more PNP for 1-h infusions, which was confirmed by the ITT analysis. Furthermore, the three patients with PNP score > 6 in this study were all treated in the 1-h group, whereas the number of performed dose reductions was nearly equal in both study arms. Only a preceding therapy with platinum, also well known to induce sensory neuropathies [14], was detected as a potentially influencing factor for the development of a PNP. However, the applied statistical tests failed to show significant differences. Although taxanes are well-known to induce PNP, it remains still unclear whether these observed neurotoxic effects are induced by PAC itself, its vehicle CrEL or both agents. Therefore, we included a pharmacokinetic examination of free and bound PAC as well as CrEL in our prospective trial. These examinations have been published by Gelderbloom *et al.* and Mross *et al.*, showing that in 1-h infusions the AUC of unbound PAC is lower than in 3-h infusions [23,24]. Concerning CrEL, a reverse effect was observed, implying that 3- compared to 1-h infusions reduces the AUC of the vehicle CrEL, which is known to be neurotoxic as well. Recently, a lack of significant accumulation of CrEL levels at doses up to 90 mg/m^2 in a weekly schedule of PAC has been described [27]. As the AUC corresponds to the exposure of free PAC or CrEL, these results can explain why the reduction of infusion time from days to short infusions has led consequently to less hematological toxicities [6]. In our patients, the number of severe hematological toxicities was comparable for both groups, implying that the effect of reduction of infusion time from 3 to 1 h on hematological toxicity is not remarkable. We observed a number of other neurological side-effects attributable to the complex of neuralgia, myalgia or arthralgia predominantly after 1-h infusions on average of week 2 (22 versus 8%). This syndrome is well known from other investigations, but has not been found to be dependent on dosage or infusion time up to now [6,7,20,28]. The pathogenesis remains still unclear. Although, these symptoms are harmless, they can induce treatment terminations as patients feel unable to bear these symptoms. In the present trial we used a dose of 8 mg dexamethasone combined with H_1/H_2 histamine blockers for premedication; only one study center applied 20 mg. Severe anaphylactic reactions only appeared in three patients with 3-h infusions. These findings correspond with about 2% of events of severe HSRs as described in the literature [6,9], so that we think that premedication with 8 mg dexamethasone is safe.

Conclusions

Neurotoxicity has featured as the most important dose-limiting toxicity in weekly PAC short infusions. From the experience of this trial we conclude that both 1- and 3-h infusions with dosages of 100 mg/m^2 are safe. The strong cumulative effect in PAC-induced peripheral neuropathy was a remarkable and unexpected result of the present study. After 12 weeks of therapy, only a quarter of the remaining patients were free of PNP. Thus, we think that the weekly evaluation of PNP by performance of the clinical score, even on an outpatient basis as an easily applicable instrument, is necessary to maintain QoL and to avoid treatment terminations due to neurotoxicity by means of early dose reductions. As the efficacy of therapy is also dose dependent, it would be desirable to develop pharmacological strategies to ensure nerve protection independent of performed dose reductions. Thereby, effects of potentially neuroprotecting agents such as venlafaxine should be investigated [29]. At present, we only partially understand the pathogenesis of therapy-induced PNP [30]. Recent findings, such as in WldS mice that are resistant to PAC-induced PNP on the basis of an altered Wallerian degeneration, might be of interest for future projects trying to reduce therapy-related neurotoxicity [31].

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