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Clinical paper

Phase I and pharmacologic study of weekly doxorubicin and 1 h infusional paclitaxel in patients with advanced breast cancer

Vinodh R Nannan Panday,[1,2] Wim W ten Bokkel Huinink,[1] Hilde Rosing,[2] Francisca J Koopman,[2] Michel JX Hillebrand,[2] Ria C Dubbelman,[1] Olaf van Tellingen,[1,2] Jan HM Schellens[1] and Jos H Beijnen[1–3]

[1]Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. [2]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Slotervaart Hospital, Louwesweg 6, 1066 EC Amsterdam, The Netherlands. [3]Department of Pharmaceutical Analysis and Toxicology, Faculty of Pharmacy, State University of Utrecht, PO Box 80.082, 3508 TB Utrecht, The Netherlands.

Doxorubicin and paclitaxel both display strong antitumor activity in the treatment of breast cancer. The optimal schedule of this combination, however, remains undefined. In this phase I and pharmacologic study, we administered weekly 12 mg/m^2 doxorubicin as a bolus infusion immediately followed by a 1 h 80 mg/m^2 paclitaxel infusion to patients with metastatic breast cancer. A total of 119 weekly courses were delivered to seven patients. Grade IV neutropenia was observed in two patients at the first dose level, thus already defining the maximum tolerated dose. Pronounced non-hematologic toxicities were mild neuropathy (grade I: 39%) and stomatitis (grade I: 19%, grade II: 8%). No signs of cardiac toxicity were observed with this dose schedule. Three partial responses were achieved in this group of heavily pretreated patients. The pharmacokinetics of paclitaxel, doxorubicin and Cremophor EL with this schedule were analyzed. Overall, the schedule was well tolerated and combined with its preliminary response rate justifies further evaluation in phase II studies. [© 1998 Lippincott Williams & Wilkins.]

Key words: Cremophor EL, doxorubicin, paclitaxel, pharmacokinetics.

Introduction

Doxorubicin is the most established member of the anthracycline antibiotics group and is very effective in the treatment of breast cancer and soft tissue sarcomas, as well as other malignancies.[1,2] The main adverse effect is cardiac toxicity, of which the incidence rises after higher cumulative doses. This risk was reduced by weekly low-dose administration of doxorubicin, while the incidence of other toxicities remained unchanged and therapeutic efficacy persisted.[3–6] Paclitaxel is a taxane derivative which favors the assembly of microtubuli with altered stability properties. Paclitaxel is associated with neutropenia, peripheral neuropathy, alopecia, nausea, mucositis and myalgia, while other adverse effects seen during the early stages were cardiac effects and hypersensitivity reactions (HSRs).[7] Furthermore, paclitaxel has shown anti-angiogenic activity.[8] Paclitaxel has demonstrated considerable effect in amongst others ovarian, head and neck, and lung cancers, and also in metastatic breast cancer patients who had already received doxorubicin either in the adjuvant setting or for metastatic disease.[7,9,10] The strong antitumor activities of each single drug, their different antitumor mechanisms and partly non-overlapping toxicities provided rationales for an adjuvant strategy in which patients received a combination of doxorubicin and paclitaxel.[11–13] At that time, it was unclear whether paclitaxel and doxorubicin should be given in sequence or concomitantly, since both antagonism as well as additive synergism was found between the two agents in preclinical studies.[14,15] From the first clinical studies, it appeared that there was more unexpected upper gastrointestinal toxicity, neutropenia and dose-limiting toxicity (DLT) mucositis when paclitaxel preceded doxorubicin than in the reverse

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Correspondence to VR Nannan Panday, Department of Pharmacy and Phamacology, The Netherlands Cancer Institute, Slotevaart Hospital, Louwesweg 6, 1066 EC Amsterdam, The Netherlands. Tel: (+31) 20 512 4737; Fax: (+31) 20 512 4753

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sequence.[16-18] Furthermore, the peak plasma concentration and clearance of doxorubicin were altered by pretreatment with 24 h paclitaxel.[18,19] This led to the suggestion that possibly drug-drug interactions or schedule dependency may occur. Once it was determined that a 3 h paclitaxel infusion was as safe as 24 h infusion while being less myelosuppressive, the attention switched to the shorter infusion regimens.[20] A high efficacy, without significant toxicity except for cardiotoxicity, nor sequence dependency by either sequence using 3 h paclitaxel infusions combined with bolus doxorubicin were observed in several studies.[21,23] Shorter paclitaxel infusion regimens would be more practical and make outpatient treatment more feasible. Paclitaxel given as a 1 h infusion is safe and convenient to be administered in the outpatient setting.[24-27] In addition, this administration schedule may yield a higher dose intensity and exposure, hopefully accompanied by less myelosuppression. The objectives of this phase I study were to determine the maximum tolerable dose (MTD) and DLT of the combination of bolus doxorubicin and paclitaxel administered as a 1 h infusion given weekly for 6 weeks, to obtain preliminary data on the activity of this combination and schedule, and to study its pharmacokinetics and pharmacodynamics in patients with advanced breast cancer.

Patients and methods

Patient selection

Patients with histologically proven measurable and/or evaluable (according to WHO criteria) metastatic breast cancer who have not had chemotherapy for metastatic disease, or one regimen of adjuvant chemotherapy not containing anthracyclines, were eligible. Previous surgery, hormonal therapy, immunotherapy or localized radiotherapy were also allowed, when at least more than 4 weeks before entry. Patients entering this study were aged between 18 and 75 years, and were non-pregnant, non-lactating females. Further eligibility criteria were: (1) World Health Organization (WHO) performance status of $\leqslant 2$ or a Karnofsky performance status $\geqslant 60$; (2) a life expectancy $\geqslant 12$ weeks. Initial laboratory requirements included an absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, total bilirubin $\leqslant 1.25$ times the upper normal limit and serum creatinine $\leqslant 1.25$ times the upper normal limit. Cardiac function had to be within normal limits, as demonstrated by left ventricular ejection fraction measurement (LVEF, measured by echocardiography or cardiac MUGA scan). Excluded from this study were patients who had received chemotherapy for metastatic disease, patients who had adjuvant treatment with anthracyclines, patients with a past or current history of neoplasm other than breast cancer, except for non-melanoma skin cancer or curatively treated carcinoma *in situ* of the cervix. Also ineligible were patients with a history of atrial or ventricular arrhythmias and/or congestive heart failure, with a history of myocardial infarction, patients with active or other serious underlying medical conditions and patients with prior allergic reactions to drugs containing Cremophor EL, such as teniposide, cyclosporin or vitamin K. Written informed consent was obtained from all patients according to the guidelines of Good Clinical Practice (GCP) and the Medical Ethics Committee of our hospital.

Study design and treatment plan

Patients were evaluated with a history and physical examination before the start of each cycle, and thereafter on day 1 of each week. All toxicities were weekly recorded according to CTC criteria. A complete blood cell count with differential was obtained twice weekly. Liver function tests, total bilirubin, alkaline phosphatase and serum creatinine were obtained every 3 weeks at each cycle. LVEF was performed every 6 weeks in each cycle. Tumor measurement was done by physical examination and with every other cycle by imaging. Doxorubicin hydrochloride (Farmitalia Carlo Erba, Brussels, Belgium) was given i.v. at a fixed dose of 12 mg/m^2 as a bolus infusion over 2-4 min, followed 1 h later by paclitaxel. Standard premedication before paclitaxel administration consisted of dexamethasone (20 mg orally, 12 and 6 h prior to paclitaxel infusion), clemastine (2 mg i.v., 30 min prior to paclitaxel) and cimetidine (300 mg i.v., 30 min prior to paclitaxel). Paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ) was supplied as concentrated sterile solution (6 mg/ml) in a 5 ml vial in polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol (1 : 1, v/v). It was diluted before use with 500 ml 5% glucose to a paclitaxel concentration not exceeding 1.2 mg/ml. Paclitaxel was administered as a 1 h infusion through an IVAC i.v. administration set with low sorbing tubing (IVAC, San Diego, CA) and an IVEX-II vented filterset (0.22 μm; Millipore, Malsheim, France) was used for in-line filtration.

The primary purpose of this study was to determine the MTD of paclitaxel given with a fixed dose of doxorubicin weekly for 6 weeks every 9 weeks. Thus,

one cycle consisted of six weekly courses, followed by a rest period of 3 weeks. The MTD was reached when at least two patients experienced any one of the subsequently following DLTs: any grade III or IV non-hematological toxicity (except for alopecia, vomiting or neuropathy), any mucositis or diarrhea of CTC grade III or greater persisting for more than 7 days or any episode of febrile neutropenia. Haematologic DLT was defined to be an ANC less than 0.5×10^9/l for more than 7 days or less than 0.1×10^9/l for more than 3 days, or thrombocytopenia CTC grade IV for more than 7 days. The weekly paclitaxel dose was only administered if it was tolerated adequately in the previous week and if ANC was 0.5×10^9/l or more. Three patients were to be entered at each dose level and dose escalations would proceed until one of three patients experienced DLT; that cohort was then expanded to more patients. The MTD was reached when out of at least six patients, two would have experienced DLT on cycle 1. The initial dose escalation plan for paclitaxel was increments of 10 mg/m^2 starting from 80 mg/m^2, while the doxorubicin dose would be kept constant at 12 mg/m^2/week. The starting dose of paclitaxel of 80 mg/m^2 was based on a recommendation as published previously.[27]

Pharmacokinetic sampling and analysis

Doxorubicin samples were collected at nine time points: immediately before the infusion, 2, 10 and 30 min after the end of the bolus infusion, and at 1, 2, 4.5, 7.5 and 18 h after the end of the infusion. Samples for paclitaxel analysis were collected prior to start, 5, 15 and 30 min during the infusion and at the end of the infusion, and 5, 15 and 30 min, and 1, 2, 3, 6, 8 and 18 h after the end of the paclitaxel infusion. Plasma was obtained by immediate centrifugation (5 min; 1500 *g*). Plasma samples were analyzed for paclitaxel by a sensitive high-performance liquid chromatographic (HPLC) method as previously described.[28] HPLC analysis in combination with fluorescence detection was used to determine doxorubicin and doxorubicinol concentrations in plasma.[29] Cremophor EL was measured by a sensitive, selective and validated reversed-phase HPLC method as designed in our laboratory by Sparreboom *et al.*[30] The concentrations of paclitaxel and doxorubicin were analyzed using the pharmacokinetic software package MW/Pharm (MEDI\WARE, Groningen, The Netherlands) and the AUCs were determined on the basis of the concentration versus time plots at each time point by the trapezoidal rule with extrapolation to infinity.

Results

Initially, three patients were entered onto this phase I study. Because DLT was observed in one of the first three patients at the starting dose level, the cohort was expanded to seven patients. Two out of seven patients suffered treatment delays in their first cycle secondary to low ANC counts. Since the MTD was already reached at the first dose level, no further dose escalations were allowed. Patient characteristics are listed in Table 1. One patient received one cycle, one patient received two cycles, three patients received three cycles and two patients received four cycles. In 12 courses, only doxorubicin without paclitaxel was administered because the ANC was 0.5×10^9/l and 1.0×10^9/l. On the request of one patient, one course was not administered at all. Thus, 119 courses delivered to these seven patients were evaluable for toxicity. The overall laboratory and clinical toxicities are listed in Table 2.

Table 1. Patient characteristics

No. of patients	7
Age (years)	
median	53
range	43–61
Performance state	
median	1
range	0–2
No. with prior hormonal therapy	6
No. with adjuvant chemotherapy	3
No. with prior radiotherapy	6
No. with estrogen receptor status	
positive	4
negative	1
unknown	2
No. with progesteron receptor status	
positive	2
negative	1
unknown	4
Dominant site of disease	
liver	3
lung	5
bone	4
soft tissue	1
Patients with no. of disease sites	
1	0
2	5
$\geqslant 3$	2
Overall weekly paclitaxel courses	
median	16
range	4–24
Overall weekly doxorubicin courses	
median	16
range	6–24

Table 2. Overall clinical and laboratory toxicities in 119 single weekly doses

Toxicity	Toxicity grade					
	0	1	2	3	4	Unknown
Anemia	85 (71%)[a]	17 (14%)	4 (3%)	0 (0%)	0 (0%)	13 (11%)
Leukopenia	70 (59%)	12 (10%)	21 (18%)	12 (10%)	4 (3%)	0 (0%)
Neutropenia	78 (66%)	14 (12%)	11 (9%)	8 (7%)	7 (6%)	1 (1%)
Trombocytopenia	119 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alopecia	19 (16%)	26 (22%)	74 (62%)			0 (0%)
Cardiac arrythmias	119 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspnea	108 (91%)	5 (4%)	5 (4%)	0 (0%)	0 (0%)	1 (1%)
Hypersensitivity reactions	118 (99%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Documented infection	109 (92%)	3 (3%)	6 (5%)	0 (0%)	0 (0%)	1 (1%)
Diarrhea	110 (92%)	6 (5%)	2 (2%)	0 (0%)	0 (0%)	1 (1%)
Constipation	89 (75%)	28 (24%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Stomatitis	86 (72%)	23 (19%)	9 (8%)	0 (0%)	0 (0%)	1 (1%)
Nausea	84 (71%)	28 (24%)	6 (5%)	0 (0%)		1 (1%)
Vomiting	105 (88%)	11 (9%)	1 (1%)	0 (1%)	0 (0%)	1 (1%)
Neuropathy	67 (56%)	47 (39%)	0 (0%)	0 (0%)	0 (0%)	5 (4%)
Skin	109 (92%)	9 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)

[a]Percentages in parentheses.

Hematologic toxicity

One of the first three patients experienced neutropenia grade IV. Subsequently, four more patients were added to this cohort and one out of these four also experienced a grade IV neutropenia in her first cycle, thus already defining the MTD. However, six of the seven grade IV neutropenias (all lasting less than 5 days) were observed within one patient. This patient was heavily pretreated, having received chemotherapy, radiotherapy and hormonal therapy. It was remarkable that the episodes of neutropenia in this patient only occurred in courses 3 and 4 of three subsequent cycles. The hematologic toxicity (expressed as percentage ANC from pretreatment value) during the cycles is shown in Figure 1. No patients required hospitalization for fever and neutropenia. No significant platelet toxicity was seen in any course. Three percent (four of 119) of the courses required red blood cell transfusions; in one case, this transfusion led to fever, which resolved spontaneously.

Non-hematologic toxicity

All seven patients developed grade II alopecia, which generally started halfway through the first cycle and was complete by the end of the first cycle. Cardiac arrhythmias were not observed in any course and cardiac toxicity, as demonstrated after each cycle by LVEF, revealed only minor or clinically insignificant changes. No significant HSRs were observed in the 119 courses, except for one course which was accompanied by mild flushing, which resolved spontaneously. Nausea, vomiting and diarrhea were generally mild. Mild to moderate constipation grade I was observed in 24% of the courses and generally responded well to laxatives. Mild grade I skin toxicity, presented by erythema and desquamations, was observed in four patients. Neurologic toxicity grade I was observed in 39% of all courses. Six of the seven patients experienced numbness and transient dysesthesias of the fingers. One out of these six patients developed mild peripheral neuropathy, having problems with knitting and buttoning. Another patient developed an impaired polyneuropathy of her feet and a more painful plexus brachialis lesion (which was preexistent) during her second cycle. Another frequently seen toxicity was stomatitis. In 19% of the courses a grade I and in 8% a grade II stomatitis was observed. In 8% of all courses a documented infection was recorded. These were due to pulmonary infection, herpes simplex type II, cystitis, sinusitis maxillaris and resolved after treatment with antibiotics or antiviral agents. Furthermore, fatigue and mild myalgia/arthralgia were common during all courses for all patients, but these were not recorded weekly.

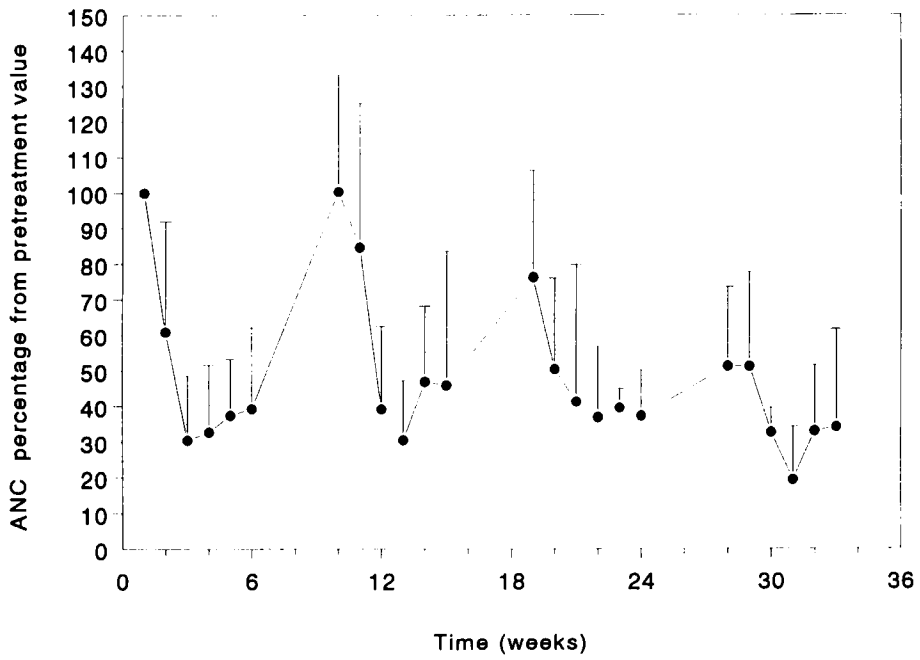

Figure 1. Mean ANC values for the patients during subsequent treatment cycles. One cycle consists of six times weekly treatment, followed by a 3 weeks rest period. x-axis, time (weeks); y-axis, ANC expressed as percentage from baseline value.

Responses

In these seven patients, three PR (no CR) were acheived. However, these three patients with PR stopped treatment at their own request after four, four and two cycles, respectively. Two patients with stable disease also stopped treatment at their own request after three cycles. One patient developed progression after an initially stable disease after three cycles and the other patient already developed progression after one cycle of this combination regimen.

Pharmacokinetics

Pharmacokinetic studies were executed during the first course of the first cycle. One patient refused to participate in the pharmacokinetic part of the study, thus pharmacokinetic data of six courses were available. Figure 2 shows the mean concentration versus time curves for paclitaxel, doxorubicin, doxorubicinol and Cremophor EL. The mean pharmacokinetic parameters for paclitaxel and doxorubicin are listed in Tables 3 and 4, respectively. The median highest measured concentration of Cremophor EL after paclitaxel administration was $0.40 \pm 0.07\%$ (v/v).

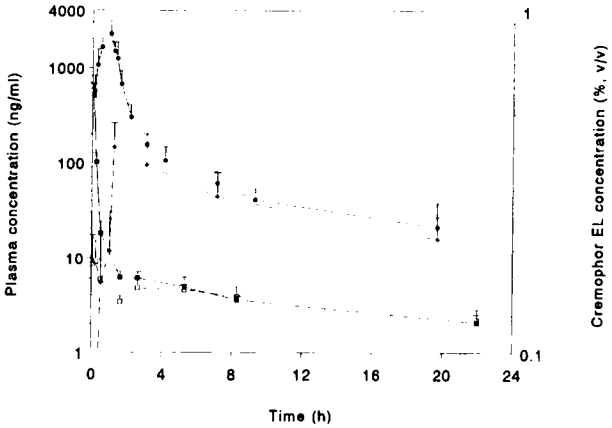

Figure 2. Concentration versus time curves for paclitaxel (●), doxorubicin (■), doxorubicinol (□) and Cremophor EL (+). x-axis, time (h); left y-axis, measured plasma concentrations (ng/ml) for paclitaxel, doxorubicin and doxorubicinol; right y-axis, measured plasma concentration (%, v/v) for Cremophor EL.

The time above the critical threshold concentration of 0.1 μmol/l of paclitaxel was 5.1 ± 1.3 h. As no dose escalations were performed due to DLT, relationships between pharmacokinetic parameters and the paclitaxel dose could not be established.

Table 3. Pharmacokinetic parameters for paclitaxel 80 mg/m^2 as 1 h infusion

Patient no.	AUC (h·μmol/l)	C_{max} (μmol/l)	Cl (l/h/m^2)	V_{ss} (l)	MRT (h)	t_{γ} (h)	T>0.1 μmol/l (h)
1	5.2	3.3	18.1	354.7	20.1	40.8	3.9
2	4.2	2.4	22.4	132.7	6.4	10.1	5.6
3	6.3	4.0	14.8	47.8	3.7	6.5	7.4
4	4.5	2.9	20.6	113.5	6.0	12.0	4.5
5	4.0	2.2	23.4	103.8	5.1	7.5	5.5
6	4.1	2.3	22.9	45.2	2.6	4.5	3.9
Mean ± SD	4.7 ± 0.9	2.9 ± 0.7	20.4 ± 3.3	132.9 ± 114.3	7.3 ± 6.4	13.6 ± 13.6	5.1 ± 1.3
CV (%)	19.1	24.1	16.2	86.0	87.7	100.0	25.5

Abbreviations: Cl=clearance; V_{ss}=volume of distribution at steady-state; MRT=mean residence time; t_{γ}=terminal half-life; CV (%)=coefficient of variance.

Table 4. Pharmacokinetic parameters for doxorubicin bolus infusion (12 mg/m^2)

Patient no.	AUC (h·μmol/l)	C_{max} (μmol/l)	Cl (l/h/m^2)	V_{ss} (l)	MRT (h)	t_{γ} (h)
1	0.24	0.05	93.5	1515	16.2	13.6
2	0.38	1.05	58.5	638	10.9	14.4
3	0.57	0.69	38.8	1249	32.2	28.9
4	0.39	0.68	57.1	720	12.6	16.9
5	0.20	0.16	111.5	1039	9.3	6.9
6	0.64	1.33	19.4	1972	10.4	93.8
Mean ± SD	0.40 ± 0.18	0.66 ± 0.50	63.1 ± 34.1	1189 ± 504	15.3 ± 8.6	29.1 ± 32.5
CV (%)	45.0	75.8	54.0	42.4	56.2	111.7

Abbreviations: Cl=clearance; V_{ss}=volume of distribution at steady-state; MRT=mean residence time; t_{γ}=terminal half-life; CV (%)=coefficient of variance.

Discussion

Several different administration schedules of paclitaxel and doxorubicin have been used, and investigations of the sequence dependency on toxicity revealed that when paclitaxel was administered before doxorubicin, this was associated with more toxicity than the reverse sequence.[16-19,21,31,32] Since the optimal dose and schedule for the administration of paclitaxel is still unknown, several infusion durations have been used for the purpose of clarifying this.[20,24-27,33,34] We undertook a phase I study in which 1 h paclitaxel was given weekly for 6 weeks, preceded by bolus doxorubicin 12 mg/m^2/week. The MTD was reached at the starting dose level, consisting of weekly 80 mg/m^2 paclitaxel and 12 mg/m^2 bolus doxorubicin. Grade IV neutropenia (ANC $<0.5 \times 10^9$/l) was observed in two out of seven patients. One of these patients was heavily pretreated and accounted for the majority of these episodes. On the contrary, doses ranging from 80 to 90 mg/m^2 of paclitaxel by 1 h infusion have been recommended previously in other studies.[25-27] However, it is important to emphasize that doxorubicin was co-administered with paclitaxel in this study, which also may have contributed significantly to the observed hematologic toxicity. In addition, the dose intensity of the schedule used in the present study was at least equal to or higher than the schedules in which paclitaxel was dosed every 3 weeks. Considering the non-hematologic toxicities, the courses were frequently accompanied by peripheral neurotoxicity and stomatitis in this study. These were principal toxicities in most other studies of the combination of paclitaxel and doxorubicin as well.[16,19,21,35] In one of these studies, dose-limiting grade III-IV mucositis was observed at a paclitaxel dose of 175 mg/m^2 and doxorubicin at a dose of 60 mg/m^2, while mucositis occurred significantly more frequently when paclitaxel preceded doxorubicin than in the opposite sequence.[16] Peripheral neuropathy grade I was found in 37.5% of cycles in one study, which is comparable to the percentage as reported here.[36] Moreover, the neurotoxicity tended to increase with the number of administered cycles, which is consistent with observations as found by others.[21,36,37] Furthermore, the non-hematologic toxicities in this study were marked by the relative absence of cardiotoxicity and HSRs. We assume that the lack of cardiotoxicity is due to the

administration of weekly low-dose doxorubicin.[3-6] In contrast, other studies in which 3 h infusions of higher paclitaxel and doxorubicin doses were used produced more marked clinical cardiotoxicity than the results found here.[21-23] On the other hand, a preliminary report described neither congestive heart failure nor myocardial contractility decrease in a study that used 1 h 200 mg/m^2 paclitaxel infusions, preceded by a short infusion of 50 mg/m^2 doxorubicin every 3 weeks.[38] In addition, no relevant clinical cardiotoxicity was observed when a 16 h time interval was maintained between the administration of bolus doxorubicin 50 mg/m^2 and paclitaxel by 3 h infusion.[39] A mild episode of a HSR occurred in the 119 courses in only one patient, which resolved spontaneously. Standard premedication was administered in all courses and the observed HSR frequency is consistent with that observed in other studies in which a 1 h paclitaxel regimen was used.[24-26] Dermatitis grade I was noted in 8%, which is comparable to the 5% that was observed in another study, but in that study transient skin rash also occurred in 47%, which was not the case here.[40] Except for vomiting grade III in one course, no other non-hematologic toxicities exceeding grade II were observed in this study.

Three PR were noted in this small group comprising seven patients. Recently, other groups reported response rates similar (39 and 43%, respectively) for single-drug weekly paclitaxel administered as a 1 h infusion in patients with metastatic breast or ovarian cancer who had failed to multiple pretreatments with hormone therapy and chemotherapy (including anthracyclines and platinum agents).[41,42] Seen from this perspective, the response rate in this small group of heavily pretreated patients does not seem to compare unfavorably.

This is the first report by our knowledge that divulges pharmacokinetic data with this dose and schedule. Considering the non-linear behavior of paclitaxel, the mean paclitaxel AUC of 4.7 ± 0.9 μmol/l·h and C_{max} of 2.9 ± 0.7 μmol/l as found here are reasonable, when compared to other studies in which higher doses of 3 h paclitaxel were given.[43,44] Furthermore, our pharmacokinetic results revealed that the mean $T \geq 0.1$ μmol/l of paclitaxel was 5.1 ± 1.3 h. This parameter is an important predictor of neutropenia and was found to be 7.6 ± 3.6 h for paclitaxel 100 mg/m^2 administered as a 3 h infusion in combination with carboplatin, as reported earlier by our group.[43] The value as found here seems realistic, since the infusion duration is also 2 h less. The doxorubicin AUC as measured in this study is comparable with dose-corrected AUC values in other single-agent doxorubicin studies.[45] However, when linear doxorubicin pharmacokinetics are assumed and corrections for the administered dose are also made, the doxorubicin AUC values that were found here are lower than those found in other combinations of doxorubicin and paclitaxel.[44] This may reflect a pharmacokinetic interaction, but cannot be established from this limited group of patients, for whom one sequence only was administered. Furthermore, after the paclitaxel infusion, a slight increase in doxorubicin and doxorubicinol concentrations was seen (Figure 2). It was demonstrated previously that a pharmacokinetic interference between doxorubicin and paclitaxel resulted in increased plasma concentrations of the anthracycline and its metabolite doxorubicinol, but this seems not to be the case here.[31] Although the main doxorubicin metabolite doxorubicinol as well as paclitaxel are both metabolized by cytochrome P450 isoenzymes, it seems unlikely that P450 enzyme induction occurs within 1 h.[19,21,46] In addition, doxorubicin was administered before paclitaxel in this study. The exact role of paclitaxel (and its metabolites) on the common elimination enzyme systems of paclitaxel and doxorubicin thus needs to be further elucidated.

It has been shown that the decreased clearance of doxorubicin and doxorubicinol may be due to the paclitaxel vehicle Cremophor EL.[47,48] The Cremophor EL dose necessary to produce such an effect is, however, 10-fold higher (5 g/m^2/h) as compared to the administered Cremophor EL dose in earlier clinical studies (0.5 g/m^2/h).[19] A relatively high dose of administered Cremophor EL may partly explain the seemingly decreased doxorubicin clearance immediately after the duration of the paclitaxel infusion (Figure 2), which is consistent with observations of others.[44] It has been suggested that this might be caused by competition of both drugs for biliary excretion mediated by P-glycoproteins (P-gp).[44] However, recent results using P-gp-deficient mice indicated that P-gp may not be essential for the hepato-biliary excretion of paclitaxel.[49] Moreover, although *in vitro* studies showed that Cremophor EL is a modulator of P-gp and reversed multidrug resistance (MDR),[50-53] Cremophor EL was not able to reverse MDR *in vivo* in tumor-bearing mouse models.[54] This is important, since Cremophor EL levels in patients were within the same order of magnitude as those in rodents receiving 2 mg/kg.[55] A direct translation of the results in rodents would indicate that the Cremophor EL concentrations in our study were probably too low to have profound effects on the clearance of doxorubicin. However, the small group of patients here lacks statistical power to detect this. Thus, further studies are warranted in order to clarify the exact role of Cremophor EL.

In conclusion, this phase I and pharmacologic study in which paclitaxel 80 mg/m^2 was given weekly for 6 weeks, preceded by bolus doxorubicin 12 mg/m^2/week, yielded DLT (grade IV neutropenia) at the first dose level. Except for mild neurotoxicity and stomatitis, other non-hematological toxicities, especially cardiotoxicity, were absent. The preliminary response rate in this very small group of heavily pretreated patients provides a rationale for performing forthcoming studies. In addition, more pharmacologic studies to elucidate pharmacokinetic interactions with this combination are eagerly awaited.

References

1. Jones RB, Holland JF, Bhardwaj S, Norton L, Wilfinger C, Strashun S. A phase I–II study of intensive-dose Adriamycin for advanced breast cancer. *J Clin Oncol* 1987; **5**: 172–7.
2. Hoogstraten B. Adriamycin in the treatment of advanced breast cancer. Studies by the Southwest Oncology Group. *Cancer Chemother Rep* 1975; **6**: 329–34.
3. Weiss AJ, Metter GE, Fletcher WS, Wilson WL, Grage TB, Ramirez G. Studies on adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiac toxicity. *Cancer Treat Rep* 1976; **60**: 813–22.
4. Praga C, Beretta G, Vigo PL, *et al.* Adriamycin cardiotoxicity: a survey of 1273 patients. *Cancer Treat Rep* 1976; **63**: 827–34.
5. Unferverth DV, Magorien RD, Leier CV, Balcerzak SP. Doxorubicin cardiotoxicity. *Cancer Treat Rev* 1982; **9**: 149–64.
6. Torti FM, Bristow MR, Howes AE, *et al.* Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. *Ann Intern Med* 1983; **99**: 745–9.
7. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **332**: 1005–14.
8. Belotti D, Vergani V, Drudis T, *et al.* The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res* 1996; **2**: 1843–9.
9. Holmes FA, Walters RS, Theriault RL. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991; **83**: 1797–805.
10. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel in metastatic breast cancer: a trial of two doses by a 3 h-infusion in patients with disease recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 1995; **87**: 1169–75.
11. Seidman AD. Single-agent use of Taxol (paclitaxel) in breast cancer. *Ann Oncol* 1994; **5** (suppl 6): S17–22.
12. Abrams JS, Vena DA, Baltz J, *et al.* Paclitaxel activity in heavily pretreated breast cancer: a NCI treatment referral cancer trial. *J Clin Oncol* 1995; **13**: 2056–65.
13. Seidman AD, Reichman BS, Crown JPA, *et al.* Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol* 1995; **13**: 1152–9.
14. Koechli OR, Sevin B-U, Perras JP, *et al.* Characteristics of the combination paclitaxel plus doxorubicin in breast cancer cell lines analyzed with the ATP-cell viability assay. *Breast Cancer Res Treat* 1993; **28**: 21–7.
15. Hahn SM, Liebmann JE, Cook J, *et al.* Taxol in combination with doxorubicin or etoposide. *Cancer* 1993; **72**: 2705–11.
16. Sledge GW, Robert N, Sparano JA, *et al.* Paclitaxel (Taxol)/Doxorubicin combinations in advanced breast cancer: The Eastern Cooperative Oncology Group experience. *Semin Oncol* 1994; **21** (suppl 8): 15–8.
17. Holmes FA. Update: the MD Anderson Cancer Center experience with paclitaxel in the management of breast carcinoma. *Semin Oncol* 1995; **22** (suppl 8): 9–15.
18. O'Shaugnessy JA, Fisherman JS, Cowan KH. Combination paclitaxel (Taxol) and doxorubicin therapy for metastatic breast cancer. *Semin Oncol* 1994; **21** (suppl 8): 19–23.
19. Holmes FA, Madden T, Newman RA, *et al.* Sequence-dependent alteration of doxorubicin pharmacokinetics by paclitaxel in a phase I study of paclitaxel and doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* **14**: 2713–21.
20. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, *et al.* European–Canadian randomized trial of Taxol in relapsed ovarian cancer: high vs. low dose and long vs. short infusion. *J Clin Oncol* 1994; **12**: 2654–66.
21. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel by 3 h-infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13**: 2688–99.
22. Gehl J, Boesgaard M, Paaske T, Vittrup Jensen B, Dombernowsky P. Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. *Ann Oncol* 1996; **7**: 687–93.
23. Dombernowsky P, Gehl J, Boesgaard M, Jensen TP, Jensen BV. Paclitaxel and doxorubicin, a highly active combination in the treatment of metastatic breast cancer. *Semin Oncol* 1996; **23** (suppl 1): 13–8.
24. Greco FA, Hainsworth JD. Paclitaxel (Taxol): phase I/II trial comparing 1-hour infusion schedules. *Semin Oncol* 1994; **21** (suppl 8): 3–8.
25. Klaassen U, Wilke H, Strumberg D, Eberhardt W, Korn M, Seeber S. Phase I study with weekly 1 h-infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. *Eur J Cancer* 1996; **32A**: 547–9.
26. Fennelly D, Aghajanian C, Shapiro F, *et al.* Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997; **15**: 187–92.
27. Loeffler TM, Freund W, Lipke J, Hausamen TU. Schedule and dose intensified paclitaxel as weekly one hour infusion. Evidence for an improved toxicity profile and response activity in pretreated solid tumors. *Proc Am Soc Clin Oncol* 1995; **14**: 470.
28. Huizing MT, Keung ACF, Rosing H, *et al.* Pharmacokinetics of paclitaxel metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol* 1993; **11**: 2127–35.
29. Beijnen JH, Meenhorst PL, van Gijn R, Fromme M, Rosing H, Underberg WJM. HPLC determination of doxorubicin, doxorubicinol and four aglycone metabolites in plasma of AIDS patients. *J Pharm Biomed Anal* 1991; **9**: 995–1002.
30. Sparreboom A, van Tellingen O, Huizing MT, Nooijen WJ, Beijnen JH. Determination of polyoxyethyleneglycerol triricinoleate 35 (Cremphor EL) in plasma by pre-column derivatization and reverse-phase high-performance liquid chromatography. *J Chromatogr* 1996; **681**: 355–62.

31. Berg SL, Cowan KH, Balis FM, *et al.* Pharmacokinetics of Taxol and doxorubicin administered alone and in combination by continuous 72-hour infusion. *J Natl Cancer Inst* 1994; **86**: 143–5.
32. Fisherman JS, Cowan KH, Noone M, *et al.* Phase I/II study of 72-hour infusional paclitaxel and doxorubicin with granulocyte colony-stimulating factor in patients with metastatic breast cancer. *J Clin Oncol* 1996; **14**: 774–82.
33. Wilson WH, Berg SL, Bryant G, *et al.* Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion. *J Clin Oncol* 1994; **12**: 1621–9.
34. Arbuck SG. Paclitaxel. What schedule? What dose? *J Clin Oncol* 1994; **12**: 233–6.
35. Amadori D, Luca Frassineti G, Zoli W, *et al.* A phase I/II study of paclitaxel and doxorubicin in the treatment of advanced breast cancer. *Semin Oncol* 1996; **23** (suppl 1): 19–23.
36. Tsavaris N, Polyzos A, Kosmas C, Giannikos L, Gogas J. A feasibility study of 1-h paclitaxel infusion in patients with solid tumors. *Cancer Chemother Pharmacol* 1997; **40**: 353–7.
37. Langer CJ, Leighton JC, Comis RL, *et al.* Paclitaxel by 24- or 1-hour infusion in combination with carboplatin in advanced non-small cell lung cancer: the Fox Chase Center experience. *Semin Oncol* 1995; **22**(4 suppl 9): 18–29.
38. Jovtis S, Mickiewicz E, Di Notto M, *et al.* No clinical cardiotoxicity associated with Taxol® (paclitaxel)-doxorubicin as first-line treatment for metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 1997; **16**: 239a.
39. Frassinetti GL, Zoli W, Silvestro L, *et al.* Paclitaxel plus doxorubicin in breast cancer: an italian experience. *Semin Oncol* 1997; **24** (5 suppl 17): S19–25.
40. Latorre A, Lorusso V, Guida M, *et al.* Paclitaxel and doxorubicin in the treatment of advanced breast cancer: a phase I/II study. *Proc Am Soc Clin Oncol* 1997; **16**: 179a.
41. Breier S, Lebedinsky C, Pelayes L, Traine G, Roffe C. Phase I/II weekly paclitaxel 80 mg/m^2 in pretreated patients with breast and ovarian cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 163a.
42. Lck HJ, Petry KU, Glaubitz M, *et al.* Weekly paclitaxel monotherapy as salvage treatment in pretreated patients with metastatic breast cancer: experience with an one hour schedule. *Br Cancer Res Treat* 1997; **46**: 59.
43. Huizing MT, Giaccone G, Van Warmerdam LJC, *et al.* Pharmacokinetics of paclitaxel and carboplatin in a dose-escalating and dose-sequencing study in patients with non-small cell lung cancer: an ECC trial. *J Clin Oncol* 1997; **15**: 317–29.
44. Gianni L, Vigano L, Locatelli A, *et al.* Human pharmacokinetic characterization and *in vitro* study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. *J Clin Oncol* 1997; **15**: 1905–15.
45. Camaggi CM, Comparsi R, Strocchi E, Testoni F, Anglelli B, Pannuti F. Epirubicin and doxorubicin comparative metabolism and pharmacokinetics. A cross-over study. *Cancer Chemother Pharmacol* 1988; **21**: 221–8.
46. Nannan Panday VR, Huizing MT, Willemse PHB, *et al.* Hepatic metabolism of paclitaxel and its impact in patients with altered hepatic function. *Semin Oncol* 1997; **24** (4 suppl 11): S34–38.
47. Webster LK, Cosson EJ, Stokes KH, Millward LK. Effect of the paclitaxel vehicle, Cremophor EL, on the pharmacokinetics of doxorubicin and doxorubicinol in mice. *Br J Cancer* 1996; **73**: 522–4.
48. Conte PF, Gennari A. Anthracyclines-paclitaxel combinations in the treatment of breast cancer. *Ann Oncol* 1997; **8**: 939–43.
49. Schinkel AH, Mayer U, Wagenaar E, *et al.* Normal viability and altered pharmacokinetics in mice lacking *mdr*1-type (drug-transporting) P-glycoproteins. *Proc Natl Acad Sci USA* 1997; **94**: 4028–33.
50. Schuurhuis GJ, Broxterman HJ, Pinedo HM, *et al.* The polyoxyethylene castor oil Cremophor EL modifies multidrug resistance. *Br J Cancer* 1990; **62**: 591–4.
51. Woodcock DM, Linsenmeyer ME, Chojnowski G, *et al.* Reversal of multidrug resistance by surfactants. *Br J Cancer* 1992; **66**: 62–8.
52. Webster L, Linsenmeyer M, Millward M, Morton C, Bishop J, Woodcock D. Measurement of Cremophor EL following Taxol: plasma levels sufficient to reverse drug exclusion mediated by the multidrug-resistant phenotype. *J Natl Cancer Inst* 1993; **85**: 1685–90.
53. Rischin D, Webster LK, Millward MJ, *et al.* Cremophor pharmacokinetics in patients receiving 3-, 6-, and 24-hour infusions of paclitaxel. *J Natl Cancer Inst* 1996; **88**: 1297–301.
54. Watanabe T, Nakayama Y, Naito M, Ohhara T, Itoh Y, Tsuruo T. Cremophor EL reversed multi-drug resistance *in vitro* but not in tumor-bearing mouse models. *Anti-Cancer Drug* 1996; **7**: 825–32.
55. Sparreboom A, van Tellingen O, Nooijen WJ, Beijnen JH. Nonlinear murine pharmacokinetics of paclitaxel results from the pharmaceutical vehicle Cremophor EL. *Cancer Res* 1996; **56**: 2112–5.

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