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ORIGINAL ARTICLE

A dose escalation and pharmacokinetic study of biweekly pegylated liposomal doxorubicin, paclitaxel and oxaliplatin in patients with advanced solid tumors

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Abstract
Purpose To evaluate the maximum tolerated doses (MTD) and the dose-limiting toxicities (DLT) of the combination of pegylated liposomal doxorubicin (PEG-LD), paclitaxel and oxaliplatin (L-OHP) administered every 2 weeks in patients with advanced solid tumors.
Methods Thirty-nine pretreated patients with advanced solid tumors received escalated doses of PEG-LD (10–16 mg/m^2), paclitaxel (100–120 mg/m^2) and L-OHP (50–70 mg/m^2) every 2 weeks. As one cycle of treatment was considered the administration of both drugs on days 1 and 15 of a 4-week cycle.
Results The MTDs were PEG-LD 14 mg/m^2, paclitaxel 120 mg/m^2 and L-OHP 70 mg/m^2. Neutropenia was the DLT in all but one case with only one episode of febrile neutropenia and no toxic deaths. Four (4%) and 13 (12%) cycles were complicated by grades 4 and 3 neutropenia, respectively. Grades 2–3 fatigue and neurotoxicity occurred in 13 and 12% of cycles, respectively. Responses were observed in patients with breast, endometrial and ovarian carcinomas.
Conclusions This is a quite well-tolerated regimen which merits further evaluation in phase II studies.

Keywords Pegylated liposomal doxorubicin · Paclitaxel · Oxaliplatin · Phase I · Solid tumors · Pharmacokinetics

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Introduction

The combinations of platinum compounds with taxanes, due to strong synergy between them, are widely used in various types of tumors including non-small cell lung cancer (NSCLC) and gynecologic malignancies [1, 2]. The addition of an anthracycline to this combination could possibly further increase its efficacy. The combination therapy offers higher response rates and longer time to tumor progression, but its greater toxicity and the lack of a clear benefit in overall survival, render it one of the most debated issues in therapy of metastatic disease [3].

Paclitaxel is one of the most active chemotherapeutic agents in various types of tumors. However, the optimal dose as well as the optimal therapeutic regimen with this compound is not yet fully defined. The more frequent weekly or biweekly administration instead of the conventional administration every 3 weeks is feasible and possibly associated with increased efficacy and improved tolerance [4, 5].

Oxaliplatin (L-OHP), a diaminocyclohexane platinum compound, has shown activity in a wide range of solid tumors including colorectal cancer, ovarian carcinoma, NSCLC, breast cancer, non-Hodgkin's lymphomas and gastrointestinal tumors [6]. It is only partially cross-resistant with cisplatin or carboplatin and devoid of severe bone marrow suppression, nephrotoxicity, or ototoxicity whereas, unlike cisplatin, its dose-limiting sensory neurotoxicity is

generally reversible [6]. In vitro studies using colon cancer cell lines have shown that the paclitaxel plus L-OHP combination had synergistic or additive effects [7]. Moreover, the combination of paclitaxel and L-OHP has been shown to be active in patients with both platinum sensitive and non-sensitive ovarian cancer [8].

The regimens containing a taxane and an anthracycline have also shown increased antitumor activity. However, these combinations are associated with high incidence of myelotoxicity and cardiotoxicity [9]. Pegylated liposomal doxorubicin (PEG-LD; Caelyx; Schering-Plough Corp., Kenilworth, NJ) was developed to improve antitumor activity of doxorubicin and to reduce its toxicity. Pegylated liposomal encapsulation reduces the plasma levels of the free drug as well as the drug delivery to normal tissues, thus decreasing the associated toxicity. Stealth liposomal drugs have a reduced clearance with prolonged circulation half-life resulting in a greater uptake of PEG-LD by tumor tissues [10]. In a phase III study, PEG-LD showed similar overall survival with doxorubicin as first-line therapy in patients with metastatic breast cancer but with a different toxicity profile. Cardiotoxicity, myelosuppression, vomiting and alopecia occurred significantly more often with doxorubicin while palmar-plantar erythrodysesthesia and mucositis occurred more often with PEG-LD [11]. Finally, in a previous phase I study from our institution, the combination of paclitaxel and PEG-LD administered every 2 weeks was feasible and associated with acceptable toxicity [12].

Based on the different mechanisms of action of paclitaxel, L-OHP and PEG-LD and their broad spectrum antineoplastic activity with favorable non-overlapping toxicity, we conducted a dose-escalation and pharmacokinetic study to determine the maximum tolerated doses (MTD) and the dose-limiting toxicities (DLT) of the combination in patients with advanced solid tumors.

Patients and methods

Patient selection

Chemotherapy-pretreated patients with histologically or cytologically confirmed advanced stage solid tumors for which there is no proven effective therapy were enrolled. Prior surgery, radiotherapy (to less than 25% of bone marrow containing bones) and chemotherapy were allowed but with a treatment-free interval of at least 4 weeks before entering the study. Other inclusion criteria were as follows: age > 18 years; a World Health Organization (WHO) performance status (PS) of 0–2; a life expectancy of at least 3 months; adequate hematologic parameters, including an absolute neutrophil count (ANC) of more than 1,500/dl, a hemoglobin level of more than 10 g/dl, and a platelet count of more than 100,000/dl; adequate hepatic (serum bilirubin < 1.5 mg/dl, SGPT/SGOT < three times normal values), renal (serum creatinine < 1.5 mg/dl), and cardiac (left ventricular ejection fraction [LVEF] $\geq$ 50%) function. Patients with brain metastases were eligible if they had been irradiated, the brain lesions were radiographically stable, and clinical improvement was evident. Patients with active infection or malnutrition (>20% weight loss during the last 3 months) or prior history of congestive heart failure or coronary artery disease were not eligible. Patients with more than NCI-CTC grade 1 peripheral neuropathy were not eligible. The presence of bidimensionally measurable disease was not required. All patients gave a written informed consent before entering the study. The study was approved by the Ethics and Scientific Committees of our Institution.

Patient characteristics

A total of 39 patients were enrolled onto the study, and their characteristics are shown in Table 1. Median age was 65 years, and 82% of the patients had a performance status (WHO) of 0–1. Twenty patients (51%) had previously received at least two other chemotherapy regimens. All patients were evaluable for toxicity assessment.

Treatment

The PEG-LD (Caelyx; Schering Plough Pharmaceuticals, Kenilworth, NJ, USA) was administered first as a 30-min i.v. infusion followed by paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ, USA) as a 3-h i.v. infusion, and last L-OHP (Eloxatin; Sanofi, Paris, France) as a 4-h i.v. infusion. The following dose levels (PEG-LD/paclitaxel/L-OHP in mg/m^2) have been evaluated: 10/100/50; 12/100/50; 12/100/60; 12/110/60; 14/110/60; 14/110/70; 14/120/70; 16/120/70. Treatment was administered every 2 weeks without growth factor support, and as one cycle of treatment was considered the administration of both drugs on days 1 and 15 of a 4-week cycle (1 cycle = 2 administrations). Premedication for paclitaxel consisted of methylprednisolone 16 mg orally 14 and 4 h and ranitidine 300 mg and dimetindene 8 mg i.v. 30 min before treatment. The prophylactic anti-emetic regimen included ondansentron 16 mg, dexamethasone 8 mg and diazepam 5 mg given i.v. 30 min before chemotherapy administration. The treatment was administered on scheduled dates if the absolute neutrophil count was $\geq$1,500 dl, platelets $\geq$100,000/dl, and all other toxicities had resolved to grade $\leq$1. Otherwise treatment was postponed for up to 3 weeks until resolution of all toxicities and then treatment was resumed with dose reduction at the previous dose level. Doses were also

Table 1 Patient characteristics

	Number of patients	%
Patients enrolled	39	
Evaluable for toxicity	39	100
Evaluable for response	33	85
Age, years		
Median	65	
Range	32–75	
Gender (male/female)	15/24	38/62
Performance status (WHO)		
0	13	33
1	19	49
2	7	18
Previous chemotherapy regimens		
1	19	49
2	7	18
≥3	13	33
Type of tumor		
Breast cancer	6	15
Adenocarcinoma of unknown primary	6	15
Endometrial carcinoma	5	13
Ovarian carcinoma	4	10
Transitional cell carcinoma	3	8
Non-small cell lung cancer	3	8
Gastric adenocarcinoma	2	5
Head and neck carcinoma	2	5
Other	8	21

reduced at the previous dose level in case of febrile neutropenia or platelet transfusion. Patients requiring more than 3-week treatment delay for any reason were withdrawn from the study, as were patients with a decline in the LVEF >15% below the baseline values or development of congestive heart failure. In case of grade 3/4 neurotoxicity the patient was also taken off study.

Dose escalation

No intra-patient dose escalation was allowed. At least 3 patients were enrolled at each dose level. If a DLT was observed in one of the first three patients, then three additional patients were enrolled at the same dose level. DLT were assessed during the first chemotherapy cycle (first 4 weeks of treatment = 2 treatment administrations). DLT was defined as the occurrence of any of the following: grade 4 hematologic toxicity lasting more than 3 days, grades 3–4 neutropenia with fever >38.2°C, grades 3–4 non-hematologic toxicity except for nausea/vomiting or alopecia and any treatment delay in the first 4 weeks of treatment due to unresolved toxicity grade > 1. Dose escalation was discontinued and the DLT dose level was reached if at least 50% of the patients treated at that level developed a DLT (e.g. at least two of three, or three of six patients). The MTD dose level was defined as the next level below the DLT dose level.

Patient evaluation

Baseline evaluation included the following: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count, blood chemistry, ECG and echocardiography or multi-gated acquisition (MUGA) scan with LVEF measurement. Computed tomography scans or abdominal ultrasounds were performed when clinically indicated. Complete blood counts with differential and platelet counts were performed once weekly or in case of grades 3–4 neutropenia or thrombocytopenia or febrile neutropenia daily until recovery. Blood chemistries, physical examination as well as a detailed toxicity questionnaire were performed before each treatment administration. The LVEF was measured by MUGA or echocardiogram at baseline and every three cycles of treatment. Toxicities were recorded according to the NCI-CTC version 2.0 criteria. Neurologic adverse effects were assessed with the use of the neurosensory section of the NCI-CTC criteria. L-OHP was discontinued in cases of persistent painful paresthesias or functional impairment. All patients who received at least one cycle of treatment were assessed for toxicity and all those with measurable disease were evaluable for response according to the RECIST criteria.

Pharmacokinetic methods

Samples for measurement of plasma levels of doxorubicin, paclitaxel and L-OHP were obtained during the first treatment administration. Sampling for doxorubicin was obtained before drug administration and at 1, 6, 24, 72 and 168 h after the beginning of infusion. Paclitaxel and L-OHP administration started at 1.5 and 4.5 h after the beginning of doxorubicin infusion, respectively. Samples for paclitaxel were collected before the drug infusion and at 1, 3, 6, 10 and 24 h after the beginning of drug infusion. L-OHP sampling was obtained before drug administration, at 2, 4, 8, 24 and 68 h after the beginning of L-OHP infusion.

Doxorubicin and paclitaxel plasma levels were measured in a LC-10A/10Avp Shimadzu HPLC system accordingly [13, 14]. For L-OHP measurements the ultrafiltrated fraction was used. Platinum levels were determined by flameless atomic absorption spectrophotometry with deuterium correction on a Schimadzu system [15]. Lower limits of quantitation were 0.05, 0.01 and 10 μg/ml, respectively.

Pharmacokinetic parameters for doxorubicin, paclitaxel and free fraction of platinum were estimated using a

non-compartmental analysis by WinNonlin program (v2.1, Pharsight Co., Palo Alto, USA). All bivariate correlations were assessed by means of Pearson's correlation coefficients (SPSS, v14.0 for Windows, USA).

Results

Dose-limiting toxicities

Table 2 indicates the dose-escalation levels, the number of patients enrolled at each level and the observed DLT during the first cycle. Neutropenia was the DLT in all but one case. Grades 2 and 3 neutropenia resulting in treatment delay on days 15 or 28 was observed in two patients each, respectively, whereas grade 4 neutropenia was observed in four patients, and grade 3 febrile neutropenia in one. Grade 3 diarrhea appeared in one patient and was the only DLT due to non-hematological toxicity. At the eighth dose level, three out of six patients developed DLT (two patients with grade 4 neutropenia and one with grade 3 febrile neutropenia) and therefore this was considered as the DLT level. The MTD, which are the doses recommended for future phase II studies, are PEG-LD 14 mg/m^2, paclitaxel 120 mg/m^2 and L-OHP 70 mg/m^2 administered every 2 weeks without growth factor support.

Hematological and non-hematological toxicity

A total of 107 cycles of treatment were administered with a median of three cycles per patient (range 1–6). The median interval between cycles was 28 days (range 28–49). Twenty-eight cycles (26%) were delayed because of hematological toxicity (11 cycles), non-hematological toxicity (2 cycles) or for reasons unrelated to the disease or treatment (15 cycles), i.e. pending imaging studies for response assessment. Tables 3 and 4 show the chemotherapy cycles complicated by grades 2–4 hematological and non-hematological toxicity, respectively.

Overall the hematological toxicity of the regimen was mild. A total of 13 (12%) and 4 (4%) cycles corresponding to 12 (31%) and 3 (8%) patients were complicated by grades 3 and 4 neutropenia, respectively. Only one episode of febrile neutropenia was observed at the last dose level. Grades 3–4 anemia or thrombocytopenia was not observed. Non-hematological toxicity was also mild. Across all dose levels the most common non-hematological toxicities were fatigue and peripheral sensory neurotoxicity. Fatigue was grade 2 in 12 cycles (11%) and grade 3 in 2 cycles (2%) corresponding to eight (20%) and two patients (5%), respectively. Similarly, neurotoxicity was grade 2 in 10 cycles (9%) and grade 3 in 3 cycles (3%) corresponding to four (10%) and three patients (8%), respectively. Grade 3 vomiting, diarrhea and mucositis were uncommon. Palmar-plantar erythrodysesthesia appeared in only one patient whereas no patient developed congestive heart failure or a reduction in the LVEF>10% of the baseline value.

Treatment delivery

The protocol-scheduled and the administered median and relative dose intensity of the PEG-LD/paclitaxel/L-OHP combination are shown in Table 5. The median cumulative dose administered was 58 mg/m^2 (range 16–165) for PEG-LD, 500 mg/m^2 (range 120–1435) for paclitaxel and 289 mg/m^2 (range 69–823) for L-OHP. Dose reduction was required in 11 cycles (10%) due to hematological (5 cycles) and non-hematological toxicity (6 cycles). All patients have discontinued the treatment for the following reasons: progressive disease (24 patients), completion of therapy (5 patients), toxicity (7 patients), refusal for further treatment (2 patients) and premature death (1 patient).

Table 2 Dose-escalation levels, number of patients (pts) enrolled and dose-limiting toxicities during the first cycle

Dose level	PEG-LD (mg/m^2)	Paclitaxel (mg/m^2)	L-OHP (mg/m^2)	No of points	DLT (No of points)
1	10	100	50	3	–
2	12	100	50	3	–
3	12	100	60	3	–
4	12	110	60	6	G2 neutropenia[a] (n = 1) G3 neutropenia[a] (n = 1)
5	14	110	60	6	G3 neutropenia[a] (n = 1)
6	14	110	70	6	G4 neutropenia (n = 1) G3 diarrhea (n = 1)
7	14	120	70	6	G4 neutropenia (n = 1) G2 neutropenia[a] (n = 1)
8	16	120	70	6	G4 neutropenia (n = 2) G3 FN (n = 1)

PEG-LD, pegylated liposomal doxorubicin; L-OHP, oxaliplatin; G, grade; FN, febrile neutropenia

[a] Denotes that the toxicity was considered a DLT because it resulted in treatment delay

Table 3 Hematological toxicity (NCI-CTC grades 2–4) in all cycles and per first cycle by dose-level

Dose level	No of cycles	Neutropenia			Anemia	Thrombocytopenia
		G2	G3	G4	G2	G3
1	7	0(0)	0(0)	0(0)	0(0)	0(0)
2	5	0(0)	0(0)	0(0)	3(2)	0(0)
3	8	0(0)	1(0)	0(0)	1(1)	0(0)
4	18	2(1)	4(1)	0(0)	0(0)	0(0)
5	20	3(1)	2(2)	0(0)	0(0)	1(1)
6	15	0(0)	1(1)	0(0)	0(0)	1(1)
7	25	4(1)	4(0)	1(1)	1(1)	0(0)
8	9	0(0)	1(1)	3(2)	0(0)	0(0)

Values are numbers of all cycles, and in parentheses the numbers of first cycles

No grade 3–4 anemia and grades 2 and 4 thrombocytopenia were recorded

Pharmacokinetics

The effects of dose escalation on major pharmacokinetic (PK) parameters of the combination are shown in Table 6. Although the interpatient variability was rather large and the studied dose ranges were narrow, both mean AUC_{all} values for doxorubicin and paclitaxel were dose-proportional as indicated by Pearson's correlation coefficients (PCC: 0.476 and 0.689, respectively) with significance level (probability, *P*) of 0.06 and 0.01, respectively. Further analysis was undertaken and the results indicated significant correlations between dose of PEG-LD and paclitaxel AUC_{all} (PCC = 0.593, $P = 0.01$, Fig. 1a) and paclitaxel Cl (PCC = −0.538, $P = 0.03$, Fig. 1b); dose of L-OHP and paclitaxel AUC_{all} (PCC = 0.645, $P = 0.01$, Fig. 1c); and dose of paclitaxel and PEG-LD AUC_{all} (PCC = 0.502, $P = 0.05$, Fig. 1d).

Table 4 Non-hematological toxicity (NCI-CTC grades 2–4) in all cycles and per first cycle by dose-level

Dose level	No of cycles	Vomiting		Diarrhea		Neurotoxicity		Fatigue		Mucositis		Allergy	Constipation	PPE
		G2	G3	G2	G3	G2	G3	G2	G3	G2	G3	G2	G2	G2
1	7	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(1)	0(0)	0(0)
2	5	0(0)	1(1)	0(0)	0(0)	0(0)	0(0)	1(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
3	8	0(0)	0(0)	0(0)	1(1)	0(0)	0(0)	2(1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
4	18	0(0)	0(0)	1(1)	0(0)	2(0)	1(0)	2(1)	0(0)	1(1)	0(0)	0(0)	2(0)	0(0)
5	20	2(1)	0(0)	0(0)	0(0)	5(0)	0(0)	7(1)	0(0)	0(0)	0(0)	0(0)	2(1)	0(0)
6	15	0(0)	1(1)	1(1)	0(0)	0(0)	1(0)	0(0)	0(0)	1(1)	2(0)	2(1)	0(0)	1(0)
7	25	5(2)	0(0)	0(0)	0(0)	2(0)	1(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
8	9	0(0)	0(0)	0(0)	1(0)	1(1)	0(0)	0(0)	2(2)	0(0)	0(0)	0(0)	0(0)	0(0)

Values are numbers of all cycles, and in parentheses the numbers of first cycles

PPE Palmar-plantar erythrodysesthesia

No grade 3 allergy, constipation, PPE or grade 2–3 edema were recorded and no grade 4 non-hematological toxicity was recorded

Table 5 The protocol-scheduled and the administered median (range) and relative dose intensity for pegylated liposomal doxorubicin (PEG-LD), paclitaxel and oxaliplatin (L-OHP) combination at the different dose levels

Dose intensities									
Dose level	PEG-LD			Paclitaxel			L-OHP		
	Scheduled mg/m^2/week	Administered mg/m^2/week	Relative %	Scheduled mg/m^2/week	Administered mg/m^2/week	Relative %	Scheduled mg/m^2/week	Administered mg/m^2/week	Relative %
1	5	4.84 (4.79–5.00)	96.7	50	50 (50–50)	100	25	25 (24.19–25.00)	100
2	6	5.95 (5.69–6.00)	99.1	50	50 (47.16–50)	100	25	24.79 (23.73–25.00)	99.1
3	6	5.48 (5.48–5.87)	91.3	50	46.67(45.65–49.49)	93.3	30	27.86 (27.39–29.33)	92.8
4	6	5.5 (4.49–6.00)	91.6	55	50.41(41.39–55.00)	91.6	30	27.50 (20.59–30.00)	91.6
5	7	6.54 (5.6–6.89)	93.4	55	47.67 (43.80–53.22)	86.6	30	26.07 (24–29,74)	86.8
6	7	6.76 (4.99–7.00)	96.5	55	54.57 (38.91–55.00)	99.0	35	34.68 (24.94– 35.00)	99.0
7	7	5.99 (5.41–6.76)	85.5	60	51.18 (43.19– 58.82)	85.3	35	29.92 (27.04–35.00)	85.4
8	8	7.42 (6.48–8.00)	92.7	60	53.71 (6.00–60.00)	89.5	35	33.30 (28.89–35.00)	95.1

Table 6 Major pharmacokinetic parameters of the combination at the different dose levels

Dose levels		I	II	III	IV	V	VI	VII	VIII
No of patients tested		(1)	(2)	(2)	(3)	(2)	(2)	(3)	(1)
PEG-LD	C_{max}	3.5	4.3 (0.7)	4.9 (2.1)	6.9 (0.7)	8.7 (0.0)	4.4 (2.1)	7.1 (1.8)	7.5
	$t_{1/2}$	78.1	19.6 (0.2)	52.0 (10.4)	42.5 (29.1)	94.0 (23.5)	52.2 (3.8)	66.1 (26.6)	29.2
	AUC_{all}	197.8	98.7 (6.2)	221.9 (42.7)	250.8 (63.0)	631.6 (37.2)	333.0 (131.0)	497.7 (266.9)	273.9
	$Cl_{(observed)}$	0.045	0.117 (0.003)	0.049 (0.007)	0.047 (0.017)	0.016 (0.003)	0.045 (0.018)	0.036 (0.025)	0.049
	$Vz_{(observed)}$	5.11	3.30 (0.05)	3.77 (1.26)	2.27 (0.88)	2.02 (0.14)	3.26 (1.13)	2.85 (1.58)	2.07
Paclitaxel	C_{max}	0.94	0.69 (0.15)	1.33 (0.75)	1.29 (0.16)	1.58 (0.16)	1.05 (0.14)	1.74 (0.40)	1.46
	$t_{1/2}$	5.2	5.9 (4.0)	3.7 (0.6)	4.3 (0.3)	2.9 (1.9)	5.0 (0.8)	5.3 (0.8)	7.2
	AUC_{all}	3.85	3.92 (0.32)	5.62 (2.34)	5.30 (0.81)	7.19 (0.25)	5.80 (0.20)	8.48 (1.19)	6.62
	$Cl_{(observed)}$	0.024	0.024 (0.005)	0.021 (0.009)	0.021 (0.003)	0.017 (0.002)	0.018 (0.001)	0.014 (0.002)	0.016
	$Vz_{(observed)}$	0.18	0.17 (0.09)	0.12 (0.06)	0.13 (0.01)	0.07 (0.04)	0.13 (0.01)	0.10 (0.01)	0.17
L-OHP	C_{max}	66.3	74.5 (11.3)	114.5 (23.8)	91.2 (21.7)	82.4 (5.1)	72.7 (1.8)	73.9 (12.0)	84.1
	$t_{1/2}$	1.8	35.0 (5.2)	22.3 (12.3)	45.0 (30.2)	14.2 (0.1)	91.4 (54.5)	15.6 (8.3)	19.1
	AUC_{all}	241.5	1618.7 (34.5)	2744.2 (1471.3)	2972.1 (1251.2)	1533.4 (113.9)	1921.1 (434.8)	1537.1 (309.8)	2279.6
	$Cl_{(observed)}$	0.250	0.016 (0.007)	0.023 (0.013)	0.023 (0.021)	0.039 (0.002)	0.013 (0.008)	0.043 (0.012)	0.028
	$Vz_{(observed)}$	0.66	0.77 (0.21)	0.52 (0.01)	0.74 (0.15)	0.79 (0.03)	1.05 (0.05)	0.82 (0.25)	0.77

Data expressed as means with standard deviations in parentheses

PEG-LD, pegylated liposomal doxorubicin; L-OHP, oxaliplatin; C_{max}, maximal drug concentration; $t_{1/2}$, terminal half-life; AUC_{all}, area under the concentration-time curve from the time of dosing to the time of the last observation; Cl, total body clearance; Vz, volume of distribution

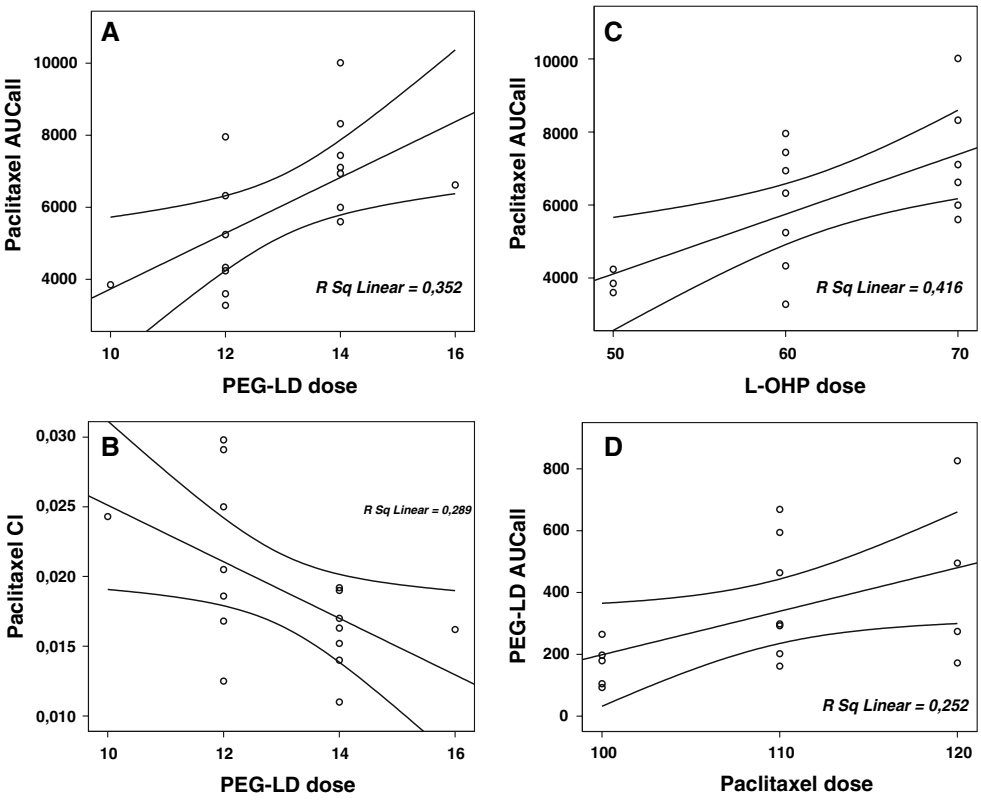

Fig. 1 Scatterplots of paclitaxel area under the concentration-time curve from the time of dosing to the time of the last observation (AUC_{all}) **a** and total body clearance (Cl) **b** values *versus* pegylated liposomal doxorubicin (PEG-LD) dose, paclitaxel AUC_{all} **c** value versus oxaliplatin (L-OHP) dose, and PEG-LD AUC_{all} **d** value *versus* paclitaxel dose

Antitumor activity

Six patients were not evaluable for response for the following reasons: death after day 15 of the first cycle (1 patient), absence of measurable disease (4 patients) and lost to follow-up (1 patient). Among 33 patients evaluable for response, six (18%) patients achieved a partial response. Stable and progressive disease were observed in six (18%) and 24 (73%) patients, respectively. The partial responses were seen in three patients with metastatic breast cancer (the first patient had previously received FEC as adjuvant treatment and Vinorelbine plus Trastuzumab as first line treatment, the second patient Vinorelbine plus Epirubicine as adjuvant treatment and for first and second line Docetaxel/Gemcitabine/Trastuzumab and Capecitabine/Trastuzumab, respectively and the third patient Docetaxel plus Epirubicin as adjuvant and the Docetaxel/Gemcitabine/Carboplatin combination as first line treatment), in two patients with endometrial carcinoma receiving third line treatment and in a patient with ovarian carcinoma receiving second line treatment. The median duration of response was 5.2 months (range 1.5–8.8) and the median time to tumor progression 2.6 (1.7–3.5).

Discussion

Although the addition of an anthracycline to platinum-taxane combinations is feasible, the associated increased toxicity is problematic especially in patients with metastatic disease for whom the goal of treatment is not the cure but rather the palliation of symptoms and perhaps prolongation of survival. In a pilot study of patients with advanced gynecological cancer, who received different regimens of platinum/anthracycline/paclitaxel combinations, the associated toxicity was significantly increased [16]. G-CSF support was required in 40% of the administered cycles while all patients experienced grade 4 neutropenia and 50% of the patients experienced grades 3–4 thrombocytopenia. Cardiotoxicity was also not negligible, since it appeared as grades 1–2 in 46% of the patients who had received doxorubicin and in 29% of those treated with epirubicin [16].

In the present study, in order to reduce toxicity, paclitaxel was administered every 2 weeks along with PEG-LD and L-OHP instead of doxorubicin/epirubicin and cisplatin/carboplatin, respectively. Neutropenia was the dose-limiting event in all but one patient. In general, neutropenia was mild, mainly of grade 2 or 3, resulting in treatment delay; however, the regimen was complicated by grade 4 neutropenia (in four patients) and febrile neutropenia (in one patient), suggesting that it should be used with caution in heavily pretreated patients. Grade 3 diarrhea was the other DLT which appeared in only one patient. Mucositis and PPE, the two main toxicities of PEG-LD, were uncommon probably due to the low dose intensity administered. Neurotoxicity was also uncommon, probably because of the low cumulative dose of L-OHP. Finally, clinical cardiotoxicity or reduction of more than 10% in the LVEF was not observed.

The pharmacokinetic profiles of combined drugs were evaluated for a total of 16 patients in eight different dose levels (Table 6). Although some of the presented data showed a rather large variability (especially for L-OHP), all the mean values are proportional to data from other published reports [13, 17, 18]. The results from the present study showed that patients' exposure to PEG-LD and paclitaxel was based on dose escalation since the mean AUC_{all} values of PEG-LD and paclitaxel were correlated well with the respective dose of the drug. Moreover, bivariate correlation analysis showed that each of the combined drugs affected PK parameters of the other co-administered drugs (Fig. 1a–d). Major PK parameters of paclitaxel reported here are changed according to PEG-LD dose escalation (Fig. 1a, b). The significant inhibition of the formation of 3′-*p*-hydroxypaclitaxel, a primary metabolite of paclitaxel, by doxorubicin could lead to significant changes in the pharmacokinetics of paclitaxel, as in our study [19]. Additionally, changes in dose levels of paclitaxel are associated well with changes of PEG-LD AUC_{all} (Fig. 1d) reported also by other groups [13]. Finally, a strong correlation between platinum levels and paclitaxel clearance is reported (PCC = −0.571, $P = 0.02$), in addition to statistically significant correlation of the same antineoplastic agent and paclitaxel AUC_{all} values (Fig. 1c). Results on paclitaxel AUC presented by Pentheroudakis et al. [20] show elevated mean levels of AUC when paclitaxel is co-administered with carboplatin compared to other studies with the same combination [21]; however, it is not possible to conclude whether or not this is due to a pharmacokinetic interaction between paclitaxel and carboplatin or due to high variability of PK values. Most importantly, Rowinsky et al. [22], in a sequence-dependent study with paclitaxel and cisplatin, reported a decreased clearance for paclitaxel, which led to an increased exposure (AUC_{all}) to the drug.

These observations clearly indicate that the toxicity of a taxane–platinum–anthracycline triplet combination could be substantially improved with the substitution of platinum and anthracycline with L-OHP and PEG-LD, respectively, using a biweekly schedule of drugs administration. Perhaps the hematological toxicity of the combination could be further improved by administering the paclitaxel as a 1-h infusion instead of the 3-h infusion used in this study [23]. In addition, it is interesting to note that although efficacy was not the primary end-point of the study, the PEG-LD/paclitaxel/L-OHP combination was active in pretreated patients with solid tumors. This encouraging activity in association

with the quite well tolerated toxicity profile of the combination justifies further evaluation of this regimen in phase II trials in patients with breast, ovarian and endometrial carcinomas.

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