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ORIGINAL ARTICLE

**Evangelos Briasoulis · Vasilis Karavasilis
Eleftheria Tzamakou · Dimitra Rammou · Kali Soulti
Christina Piperidou · Nicholas Pavlidis**

Interaction pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel

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Abstract *Purpose*: To investigate the pharmacokinetics of polyethylene glycol-coated liposomal doxorubicin (PLD, Caelyx) when given as a single agent and in combination with the taxanes paclitaxel or docetaxel in humans. *Methods*: The plasma kinetics of PLD were studied in 19 cancer patients treated with PLD every 4 weeks combined with either paclitaxel (on a weekly basis in seven and as a single infusion in three patients) or docetaxel (weekly in seven and as a single infusion in two). Plasma concentrations of PLD were quantified in two sets of samples per patient to compare the same pharmacokinetic parameters in each subject when treated with single-agent PLD and again with the combination. Total doxorubicin concentrations in plasma were quantified by HPLC. Pharmacokinetics were evaluated by noncompartmental analysis and the data obtained were compared for differences by a matched-pairs nonparametric test. *Results*: Coadministration of paclitaxel produced a median/mean 54/80% increase in PLD AUC_{inf} (95% confidence interval 23% to 136%, $P = 0.002$). The observed increase was consistent among all subjects. PLD clearance was also decelerated in the presence of paclitaxel ($P = 0.013$) while other pharmacokinetic parameters were affected modestly. A small increase in the AUC of PLD was observed in the docetaxel/PLD arm (mean increase 12%, $P = 0.039$) while PLD clearance decreased marginally and other pharmacokinetic parameters remained unaffected. AUC extrapolated to infinity was below 8% in both arms. *Conclusions*: This study showed the presence of a pharmacokinetic interaction that led to higher plasma concentrations of PLD when combined with paclitaxel and to a minor extent when combined with docetaxel. This pharmacokinetic information may be of value when planning combination therapies of PLD with taxanes.

Keywords Pharmacokinetics · Paclitaxel · Docetaxel · Pegylated liposomal doxorubicin

E. Briasoulis (✉) · V. Karavasilis · E. Tzamakou
D. Rammou · N. Pavlidis
Medical Oncology Department,
Ioannina University Hospital,
45500 Ioannina, Greece
E-mail: ebriasou@otenet.gr
Tel.: +30-265-1099394
Fax: +30-265-1099394

K. Soulti · C. Piperidou
Laboratory of Analytical Chemistry,
European Environmental Research Institute,
Ioannina, Greece

Introduction

The combination of doxorubicin with taxanes stands as a valid therapeutic option in the treatment of breast cancer and other solid tumors [1, 2, 3]. Yet concerns exist regarding the potential for increased cardiotoxicity with doxorubicin/paclitaxel combinations as compared to doxorubicin alone [4, 5, 6, 7]. This seems to be somehow connected to an interaction in the pharmacokinetics of the two drugs that produces higher systemic exposure to both doxorubicin and the metabolite doxorubicinol [8, 9]. Such an interaction has not been recognized for the docetaxel/doxorubicin combination [10].

Polyethylene glycol-coated liposomal doxorubicin (PLD, Caelyx) is a formulation of doxorubicin in polyethylene glycol-coated liposomes primarily developed to optimize the patients' quality of life and minimize toxicity. Claimed advantages for these pharmaceutical formulations are favorably altered pharmacokinetics, passive tumor trapping due to an enhanced permeability and retention effect of tumor vessels, and abrogation of unacceptable clinical toxicity. Because of its favorable clinical profile, PLD is gaining acceptance as a useful alternative to nonencapsulated standard doxorubicin [11, 12, 13, 14]. Combinations of PLD with taxanes have also been investigated clinically [15] but information on possible pharmacokinetic interactions of these compounds is not yet available.

The aim of this study was to explore alterations in the pharmacokinetics of PLD when combined with paclitaxel or docetaxel. To our knowledge this is the first published study to deal with the effects of the two taxanes upon the plasma kinetics of PLD.

Materials and methods

Study and subjects

This was an open-label drug interaction study designed to run as part of two parallel clinical phase I trials of PLD combined with either paclitaxel or docetaxel. The primary end-point of this inter-trial study was to investigate the pharmacokinetics of PLD when given as a single agent and in combination with the taxanes paclitaxel or docetaxel in humans. Both clinical protocols were approved by the local institutional review board and were conducted between January 1999 and August 2001 at the Oncology Department of the Ioannina University Hospital [16, 17]. A total 19 patients with a median age 65 years (range 55–77 years) with normal kidney and liver function and a variety of solid tumors were enrolled. All subjects provided signed informed consent. Ten patients were treated with paclitaxel plus PLD and nine patients received docetaxel plus PLD (Table 1).

Treatment

PLD was first given as a single agent in all patients. It was readministered 4 weeks later in combination with one of the taxanes. PLD was diluted in 250 mg D5W and infused intravenously over 1 h. In combination, it was followed immediately thereafter by a 1-h infusion of docetaxel or low-dose paclitaxel. The duration of infusion of standard-dose paclitaxel was 3 h. In the weekly regimens taxanes were readministered on days 8 and 15 followed by a 1-week rest. Treatment courses were recycled every 28 days.

Pharmacokinetics were investigated at the defined optimal doses in the two parallel studies. These were 30 or 35 mg/m^2 PLD administered every 4 weeks and combined with weekly paclitaxel 70 mg/m^2 or weekly docetaxel 30 mg/m^2. To better define alterations in the pharmacokinetics of PLD administered with taxanes, we investigated the pharmacokinetics of PLD in five patients treated with PLD 35 mg/m^2 combined with conventional doses of either paclitaxel (175 mg/m^2, three patients) or docetaxel (60 mg/m^2, two patients) administered every 28 days. Antiallergic medication was always given before administration of taxanes. This consisted of 32 mg oral methylprednisolone the day before, and a triplet of 16 mg dexamethasone, 0.1 mg/kg dimethindene maleate and 100 mg ranitidine administered intravenously 30 min prior to treatment.

Table 1 Demographics (*PLD* polyethylene glycol-coated liposomal doxorubicin, *wP* weekly paclitaxel, *sP* single shot paclitaxel, *wD* weekly docetaxel, *sD* single shot docetaxel)

Patients studied	19
Age (years)	
Median	65
Range	55–77
Gender	
Male	10
Female	9
PS	
Median	1
Range	0–2
Tumor type	
Carcinoma of unknown primary	6
Lung	4
Head and neck	2
Breast	2
Ovarian	2
Renal	1
Sarcoma	1
Bladder	1
Treatment (mg/m^2)	
PLD30–wP70	4
PLD35–wP70	3
PLD35–sP175	3
PLD30–wD30	2
PLD35–wD35	5
PLD35–sD60	2

Blood sampling and analysis

Each patient was sampled twice, initially during the administration of PLD as a single agent and again during the first cycle of the combination. Heparinized blood (5 ml each) was collected from patients at the following time points: 0 (predose), 0.15, 0.25, 0.5, 1, 2, 3, 8 and 24 h, and also on the 3rd, 7th, 14th and 21st day after infusion of PLD. Blood samples were processed for plasma, centrifuged at 2500 *g* for 10 min at 4°C and stored deep-frozen at approximately −20°C until analyzed. Samples were analyzed for total plasma doxorubicin at the Laboratory of Analytical Chemistry, European Environmental Research Institute, Ioannina, Greece.

A reversed-phase high-performance liquid chromatographic (HPLC) assay developed by Gabizon et al. was used to quantify doxorubicin, the active component of PLD [18, 19]. In brief, a 0.4 ml aliquot of plasma was prepared for analysis by adding 0.4 ml isopropanol, 0.4 ml chloroform, 0.5 g ammonium sulfate, and internal standard (daunorubicin). The resulting mixture was centrifuged for 15 min at 10,000 rpm and the supernatant solution was decanted and evaporated to dryness under nitrogen at 30°C. The samples were stored dry at −20°C.

For analysis, the concentrated samples were reconstituted in 200 µl isopropanol and were injected at ambient temperature into the HPLC system. The system was a Shimadzu LC-10AD HPLC unit equipped with an RF-10Axl fluorescence detector (Shimadzu, Kyoto, Japan), and a reverse-phase column (LiChrospher RP-8, 5 µm; Agilent Technologies, Palo Alto, Calif.) measuring 150×4.6 mm. The mobile phase was an acetonitrile/water (4:6 v/v) mixture adjusted to pH 2.60 with perchloric acid. Doxorubicin was detected by fluorescence at 470 nm excitation and 590 nm emission wavelengths and the data were processed on a PC/HP Vectra 486/33 VL equipped with LC workstation class-LC10 software (Kyoto, Japan). All recorded values were based on the internal standard.

The linear range of the assay was established as 0.10–7.50 µg/ml, with a lower limit of quantitation of 0.05 µg/ml. The within-day coefficient of variation was less than 9% and the overall deviation from nominal values was less than 8%.

Pharmacokinetics and statistics

Pharmacokinetics of PLD were determined according to standard noncompartmental equations using the WinNonLin computer program, version 2.1 (Pharsight Corporation, Palo Alto, Calif.). The area under concentration-time curve from time zero to infinity (AUC_{inf}) was calculated using the linear trapezoidal rule from time zero to the time corresponding to last sampling point (C_{last}) and extrapolation to infinity, based on the last observed concentration. The total plasma clearance and terminal half-life ($t_{1/2}\lambda z$) were calculated using the equations: $Cl = dose/AUC_{inf}$ and $t_{1/2}\lambda z = \ln 2/lz$

(where lz is a first-order rate constant associated with the terminal log-linear portion of the curve, estimated via linear regression of time vs log concentration).

Statistical analysis was done using the Prism 4 for Windows program (GraphPad Software, Calif.). Pharmacokinetic values for the two arms (single agent PLD vs combination) were compared for differences by the Wilcoxon matched-pairs nonparametric test and two-tailed *P* values were determined. *P* values less than 0.05 were considered statistically significant.

Results

A total of 19 patients (9 women and 10 men) were enrolled and completed the study. Plasma concentrations of PLD were quantified in 38 sets of samples (two sample sets per patient). The predefined precision criteria of the analytical assay were met during analysis of the test plasma samples (coefficient of variation $< 9\%$). Overall, all pre-treatment (T0) samples in single PLD and combination therapies gave zero values and the derived pharmacokinetic parameters showed considerable interindividual variability. Summary pharmacokinetic data presented as mean values per dose and regimen are shown in Table 2.

PLD plus paclitaxel

AUC Ten patients entered the paclitaxel-PLD study. Coadministration of paclitaxel had a substantial effect on the pharmacokinetics of PLD producing a median/mean 54/80% increase in the AUC_{inf} of PLD (95% confidence interval 23% to 136%; Figs. 1 and 2, Table 3). The percentage of the AUC extrapolated to infinity was low: mean 7.1% for the single PLD arm and 8.8% for the combination. The increase in exposure to

Table 2 Pharmacokinetics of PLD as a single agent and in combination grouped by treatment regimen (*wP* weekly paclitaxel, *sP* single shot paclitaxel, *wD* weekly docetaxel, *sD* single shot docetaxel; $t_{1/2}$ elimination (terminal) half-life, AUC_{inf} area under concentration-time curve from time zero to infinity, *Cl* clearance, C_{max} maximum concentration)

Study	Treatment	No. of patients	AUC_{inf} (mg·h/l)		Cl (ml/h)	$T_{1/2}$ (h)	C_{max} (mg/l)
			Mean	SD			
Paclitaxel	PLD30	4	1323.0	690.5	27.1	85.0	14.3
	PLD30 + wP70		2189.0	1082.0	16.4	141.9	16.2
	PLD35	3	1567.0	525.6	20.6	61.5	15.2
	PLD35 + wP70		2486.0	724.2	15.9	79.3	18.3
	PLD35	3	1816.0	583.6	18.0	51.3	14.8
	PLD35 + sP175		3583.0	2239.0	11.0	121.3	17.9
Docetaxel	PLD30	2	1400.0	145.8	21.6	85.1	12.4
	PLD30 + wD30		1438.0	583.7	22.7	68.9	16.3
	PLD35	5	2410.0	790.4	16.1	77.3	20.4
	PLD35 + wD30		2798.0	1135.0	14.0	83.4	19.5
	PLD35	2	2339.0	720.4	13.5	70.4	23.0
	PLD35 + sD60		2776.0	824.8	11.3	77.3	22.4

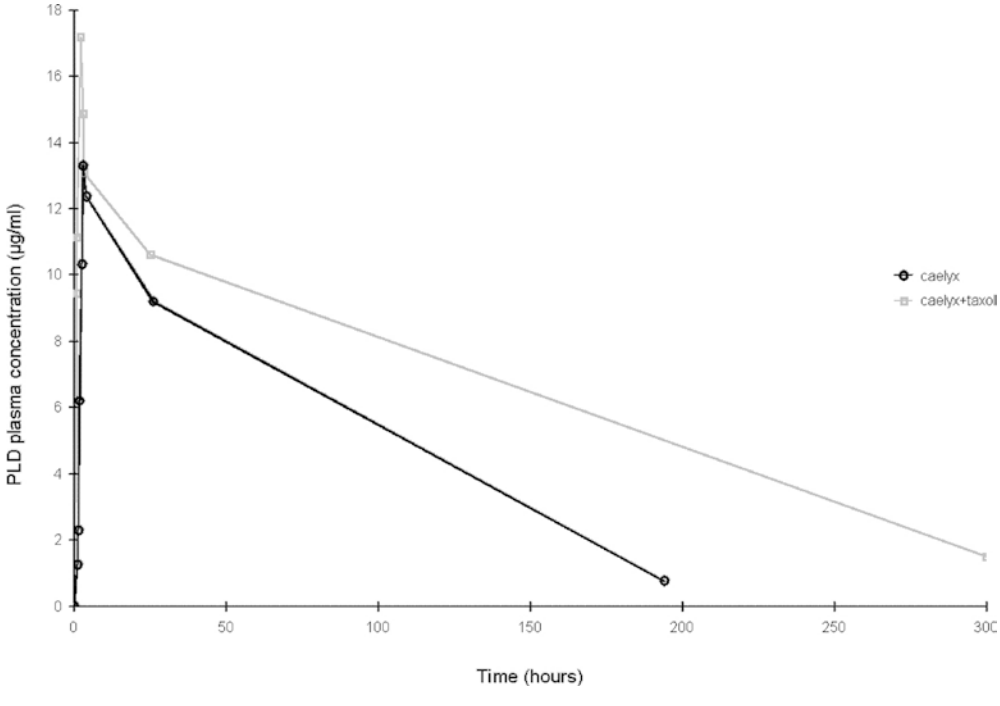

Fig. 1 Representative graph showing the time course of plasma concentrations of doxorubicin (PLD) in a patient treated with 30 mg/m^2 PLD as a single agent and in combination with 70 mg/m^2 weekly paclitaxel

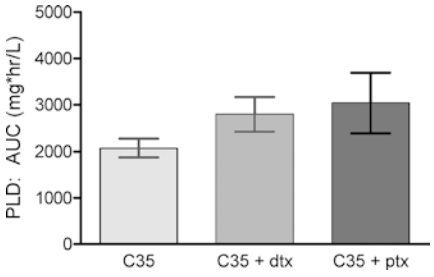

Fig. 2 AUC_{inf} values (means ± SEM) of doxorubicin plasma levels in patients treated with 35 mg/m^2 PLD given as single agent (*C35*, $n=13$) and in combination with docetaxel (*C35 + dtx*, $n=7$) or paclitaxel (*C35 + ptx*, $n=6$)

Table 3 Proportional (%) change in PLD AUC_{inf} in the presence of taxanes in patients treated with the PLD/paclitaxel and PLD/docetaxel combinations

	Proportional (%) change in PLD AUC_{inf}	
	In combination with paclitaxel	In combination with docetaxel
Median	54	20
Mean	80	12
95% CI	23 to 136	−0.04 to 25
P value[a]	0.002	0.039

[a]Two-tailed *P* values, Wilcoxon matched-pairs' test

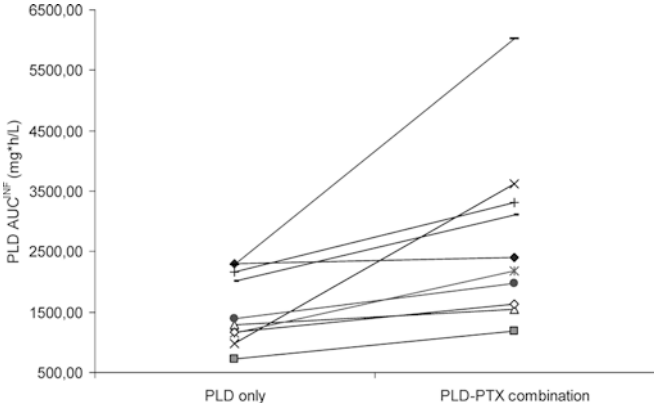

Fig. 3 Individual per patient changes in PLD AUC_{inf} in the presence of paclitaxel. Wilcoxon signed rank's test for difference: $P=0.002$. There are two outliers which represent a patient treated with PLD 35 mg/m^2 and paclitaxel 175 mg/m^2 (*top line*) and a patient treated with PLD 30 mg/m^2 in combination with weekly paclitaxel 70 mg/m^2 (*bottom line*)

PLD was consistent among all subjects and the differences observed were of strong statistical significance when analyzed by the Wilcoxon matched-pairs test (two tailed $P=0.002$; Fig. 3).

The increase in AUC_{inf} of PLD was higher (mean/median increase +102%) in two patients treated with 175 mg/m^2 paclitaxel, which is considered the standard dose for three weekly administrations of paclitaxel; however, the small number of patients did not allow statistical consideration of the difference.

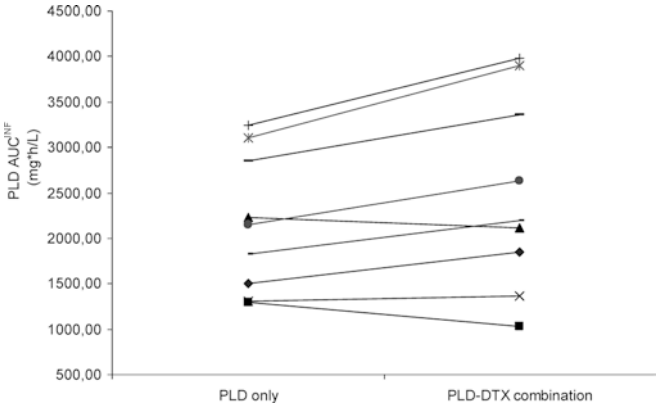

Fig. 4 Individual per patient changes in the AUC_{inf} of PLD in the presence of docetaxel. Wilcoxon signed ranks test for difference: $P=0.039$

Clearance The clearance of PLD was reduced in all subjects in the presence of paclitaxel by a mean value of −71% (95% CI −8% to −133%). This decrease was statistically significant ($P=0.013$).

T1/2, Tmax and Cmax The terminal phase half-life of PLD was prolonged by coadministration of paclitaxel (67 h with single-agent treatment vs 116 h with the combination) but this difference failed to reach statistical significance ($P=0.10$). In contrast, a modest (14 vs 17 mg/l) although significant increase in C_{max} of PLD in combination with paclitaxel was observed ($P=0.02$). The C_{max} was achieved 1 h after the end of PLD infusion with single-agent treatment and with the combination (mean T_{max} 2 h).

PLD plus docetaxel

AUC A statistically significant increase in the AUC of PLD was also observed in the docetaxel/PLD study ($P=0.039$). However, this was small (median/mean increase 20/12%) and was not seen in all subjects (Fig. 4). The mean AUC_{inf} was only 5.3% for the single PLD arm and 4.9% for the combination.

Clearance The clearance of PLD decreased marginally in combination with docetaxel (mean change −16%, 95% CI −0.6% to −32%; Table 2). This difference was not statistically significant when all cases were pooled ($P=0.16$), but marginal statistical significance was reached when only data from patients treated with the same PLD dose (35 mg/m^2) were analyzed (Wilcoxon test, $P=0.013$).

T1/2, Tmax and Cmax The elimination half life of PLD was not significantly altered by administration of docetaxel (mean values 77.5 and 78.8 h, respectively, for the single agent and the combination; $P=0.8$). The values of C_{max} were practically the same in the two arms (19.2 vs 19.5 mg/l) and occurred 90 min after infusion with single-agent treatment and with the combination (mean T_{max} 2.30 h).

Discussion

The recognition of drug–drug pharmacokinetic interactions is important in considering the impact such interactions might have on optimizing dose scheduling of cytotoxic agents in cancer combination chemotherapies. In this study we investigated alterations in the pharmacokinetics of PLD when combined with paclitaxel or docetaxel.

The formulation of doxorubicin as PLD is known to result in a prolonged circulation time, passive entrapment into cancer tissues and mild toxicity [20, 21]. Combinations of PLD with taxanes have been investigated clinically with the same therapeutic targets as combinations of taxanes with conventional doxorubicin [22]. However, the pharmacokinetic behavior of liposomal doxorubicin when combined with taxanes has been inadequately investigated. Only the pharmacokinetics of paclitaxel have been studied and have been found to be unaffected by PLD [23].

The most remarkable finding of our study was the demonstration that coadministration of paclitaxel produced a significant increase in plasma concentrations of PLD. This is in line with what is known for free doxorubicin. It has been shown that paclitaxel induces significant alterations in the plasma kinetics of doxorubicin leading to higher systemic exposure to this agent [8, 9]. Modest alterations in the plasma kinetics of PLD were found to occur with docetaxel. Pharmacokinetic studies have also shown minimal alterations in the pharmacokinetic behavior of both free doxorubicin and docetaxel when used in combination [24]. Whether the differences in pharmacokinetic interaction of PLD with the two taxanes are related to the different formulation vehicles used is unknown. However, the formulation vehicle (Cremophor) of paclitaxel seems to have some role in this pharmacokinetic interplay [25, 26].

Paclitaxel was also found to induce alterations in the majority of pharmacokinetic parameters of PLD and interestingly in C_{max}. This finding is not easily explained, as with intravenous administration of conventional nonencapsulated drugs, the maximum concentration in serum is normally reached at the end of the infusion time, that is before the administration of the combination agent. However, in our study C_{max} was reached 2 h after initiation of infusion, almost at the time of completion of administration of the taxane. This is in accordance with other studies that have also shown that the maximum concentration of liposomal encapsulated drugs in the blood comes late and is usually achieved after completion of the intravenous infusion [21, 27].

The findings of this study are of main interest in the perspective of prolonged therapies and drug accumulation issues. Systemic exposure to doxorubicin is known to prohibit the free combination or addition of treatments associated with an increased risk of cardiac toxicity such as novel HER2/cerbB-targeted therapies that are emerging for the treatment of prolonged disease suppression [28, 29, 30]. Cumulative doses of doxorubicin higher than 450 mg/m^2 are known to be associated with an increased rate of heart failure [31], but PLD carries a considerably reduced risk and can safely be given as a single agent at higher doses [32, 33]. However, increased exposure to liposomal doxorubicin should be encountered when treating patients with PLD plus paclitaxel combinations. The observed high incidence of toxicity observed at relatively low doses of PLD when coadministered with paclitaxel and less with docetaxel can readily be explained by the findings in this study [22, 34].

It could be argued that a weakness of this study was the relatively small number of patients enrolled. However, the design of this study should be considered adequate for investigating pharmacokinetic interaction between the two drugs, because all patients acted as their own control and the same pharmacokinetic parameters of PLD were compared in each subject. Moreover, the percentage of the AUC_{inf} was very low due to the extended sampling time. Carry-over effects could also be argued as a potential problem because PLD was in all cases given first followed by the combination. However, the 4-week time interval between the single PLD treatment and the combination and the zero values of pretreatment samples testify against such a consideration.

In conclusion, we found that paclitaxel induces significant and potentially meaningful alterations in the disposition of PLD which translates to increased systemic exposure to liposomal encapsulated doxorubicin. This effect was minor in regard to docetaxel. We suggest that an at least 50% higher exposure to doxorubicin for every given dose of PLD when combined with paclitaxel and a less than 20% increase when combined with docetaxel should be taken into account to achieve safe and optimal clinical use of these combinations.

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