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CLINICAL TRIAL REPORT

**António Moreira · Rosário Lobato · José Morais
Sandra Silva · Josefa Ribeiro · Ana Figueira
Dina Vale · Carla Sousa · Fátima Araújo
Aires Fernandes · João Oliveira
José Luis Passos-Coelho**

Influence of the interval between the administration of doxorubicin and paclitaxel on the pharmacokinetics of these drugs in patients with locally advanced breast cancer

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Abstract *Purpose*: The combination of bolus doxorubicin followed by a 3-h infusion of paclitaxel has high antitumor activity in patients with metastatic breast cancer, but is limited by unexpected cardiac toxicity. In contrast, the administration of the two drugs 16 h apart has similar antitumor activity but less cardiac toxicity. The purpose of this study was to compare the pharmacokinetics of these drugs when doxorubicin administration preceded paclitaxel by 30 min or by 24 h. *Patients and methods*: Women with locally advanced breast cancer were treated with doxorubicin (60 mg/m^2 i.v. bolus) followed 24 h later by paclitaxel (200 mg/m^2 i.v. over 3 h) for six cycles (four before and two after surgery). In one of the first two cycles doxorubicin preceded paclitaxel by 30 min instead of 24 h, with plasma sampling for pharmacokinetic analysis up to 48 h. Determination of drug levels in plasma was done by HPLC. *Results*: A total of 28 patients were included. No clinical cardiac toxicity was observed but five patients discontinued doxorubicin-paclitaxel treatment after four cycles because of a decrease in LVEF of at least 15% from baseline or to less than 50%. While paclitaxel pharmacokinetics were not changed, there was a 30% and an 80% increase in the AUC_{0-24h} for doxorubicin and doxorubicinol, respectively, when the drugs were administered 30 min instead of 24 h apart. Even when paclitaxel was given 24 h after doxorubicin, there was a rebound 24% increase in the plasma concentration of doxorubicinol. *Conclusions*: Paclitaxel interferes with the pharmacokinetics of doxorubicin leading to higher systemic exposure to both doxorubicin and doxorubicinol, which is more evident when the plasma concentration of the anthracyclines is higher. This interference may explain the higher incidence of cardiac toxicity observed when the two drugs are administered within a short interval.

Keywords Breast cancer · Cardiac toxicity · Doxorubicin · Paclitaxel · Pharmacokinetics

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A. Moreira (✉) · J. Ribeiro · A. Figueira · D. Vale · C. Sousa
F. Araújo · A. Fernandes · J. Oliveira · J.L. Passos-Coelho
Department of Medical Oncology,
Instituto Português de Oncologia,
Rua Prof. Lima Basto, 1093 Lisbon Codex, Portugal
E-mail: jlpassoscoelho@ipolisboa.min-saude.pt
Tel.: +351-21-7229891
Fax: +351-21-7229851

R. Lobato · J. Morais · S. Silva
Faculdade de Farmácia, Lisbon, Portugal

Introduction

Anthracyclines and taxanes are among the most active cytotoxic drugs in breast cancer treatment. However, in patients with newly diagnosed metastatic breast cancer, the combination of bolus doxorubicin followed immediately by paclitaxel (over 3 h) has high antitumor activity but unexpected cardiac toxicity [4, 5]. In contrast, the administration of the two drugs 16 h apart has similar antitumor activity but less cardiac toxicity [1]. The interference of paclitaxel in the pharmacokinetics of doxorubicin, when the two drugs are administered within a short interval, may explain such cardiotoxicity [6]. Therefore, we studied the pharmacokinetics of doxorubicin, of its main metabolite doxorubicinol and of paclitaxel in 28 patients with locally advanced breast cancer treated with doxorubicin followed, 30 min or 24 h later, by paclitaxel to evaluate the influence of the interval between the administration of the two drugs on the pharmacokinetic parameters.

Patients and methods

Clinical protocol

Eligibility criteria included: cytologically or histologically documented non-inflammatory locally advanced breast cancer (T3 N any, T any N2 or T4a–c N any); age not more than 60 years;

ECOG performance status less than 2; absolute neutrophil count $>1.5\times10^9$/l and platelet count $>100\times10^9$/l; bilirubin, AST and ALT less than two times the upper limit of normal and creatinine <1.5 mg/dl; left ventricular ejection fraction (LVEF) $>50\%$ by multiple gated angiogram (MUGA); no prior chemotherapy; and written informed consent. The study was approved by the local institutional review board and complied with the principles of the Declaration of Helsinki (1996 version).

Patients received six cycles of chemotherapy, four before a modified radical mastectomy and two after surgery. Radiation therapy to the chest wall and regional lymph nodes was administered after completion of chemotherapy and patients with positive or unknown hormone receptor status received tamoxifen.

The chemotherapy regimen consisted of doxorubicin 60 mg/m^2 i.v. over 5 min on day 1, followed by paclitaxel 200 mg/m^2 i.v. over 3 h, 24 h later on day 2. Paclitaxel premedication was prednisolone 25 mg orally 12 h before paclitaxel and hydrocortisone 250 mg, ranitidine 50 mg and clemastine 2 mg, all i.v., 30 min before paclitaxel. To allow the pharmacokinetic analysis, in one of the first two cycles patients received both drugs on day 1, with doxorubicin preceding paclitaxel by 30 min (scheme A) in contrast with the remaining cycles in which doxorubicin preceded paclitaxel by 24 h (scheme B). The allocation of treatment was performed randomly to minimize carry-over effects.

Blood cell counts were determined on days 1, 8 and 15 of each cycle and serum glucose, electrolytes, renal and liver function and coagulation tests were performed before each cycle. LVEF was measured at baseline, after 4 and 6 cycles of treatment, and after radiation therapy. All patients are assessable for response. Clinical and radiological evaluation was performed before the first and after the fourth cycle of chemotherapy. Standard response criteria were used. Complete response was defined as the clinical and mammographic disappearance of the breast tumor and axillary lymph nodes for at least 1 month.

Reasons for study withdrawal were: decrease in LVEF to less than 50% or an absolute decrease of at least 15% compared to pretreatment value, clinical manifestations of congestive heart failure, grade 3 or 4 extrahematopoietic toxicity (excluding alopecia), and disease progression. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

Pharmacokinetic analysis

Pharmacokinetic analysis of doxorubicin, doxorubicinol and paclitaxel was performed during the administration of the first two cycles of chemotherapy. When both drugs were administered on day 1 (scheme A), blood samples were obtained before the infusion, at 3.5 h (end of paclitaxel infusion), and at 6, 9, 12, 24 and 48 h after the beginning of doxorubicin administration. When doxorubicin was administered 24 h before paclitaxel (scheme B), blood samples were obtained before doxorubicin and at 3, 6, 9, 12, 24 (before paclitaxel infusion), 27 (end of paclitaxel infusion), 30, 33, 36 and 48 h after the start of doxorubicin administration. Each 10-ml blood sample was collected into a heparinized tube, placed on ice and rapidly centrifuged to separate the plasma; the plasma was then kept frozen (–20°C) until analysis. To define better the pharmacokinetics of doxorubicin and paclitaxel in the first 3 h and during the terminal portion of the elimination phase, extra blood samples were collected from the last 12 patients at 30, 60, 90 and 120 min, and 72 h after the beginning of doxorubicin infusion.

Drug analysis in plasma by high-pressure liquid chromatography (HPLC)

Reagents and drugs

Doxorubicin, doxorubicinol, daunorubicin, paclitaxel (Taxol, BMY-45622) and methylpaclitaxel (methyl-Taxol, BMS-183061) were kindly supplied by Bristol-Myers Squibb Co. All chemicals and solvents were analytical or HPLC grade (Merck, Darmstadt, Germany) and water was deionized.

Instrumentation

Doxorubicin and doxorubicinol. Analysis by HPLC was performed using a Shimadzu LC-6 A pump equipped with a Shimadzu RF-551 spectrofluorometric detector (excitation wavelength 227 nm; emission wavelength 560 nm). A 30-cm μBondapak C18 column (Waters Company, Milford, Mass.) and a mobile phase of ammonium acetate (pH 5.0)/acetonitrile/methanol (66:24.5:9.5) with tetrahydrofuran (0.5%) pumped at 1.5 ml/min were also used. Data acquisition was performed with a Hewlett Packard 3390 A integrator.

Paclitaxel. An isocratic pump (Hewlett Packard series 1100) equipped with a variable wavelength UV detector (set at 227 nm) was used. A Nova-Pak C18 column (Waters) and a mobile phase of acetonitrile/water (45:55) pumped at 1.0 ml/min were also part of the system. Detector and pump control as well as data acquisition and processing were performed by Chemstation Hewlett Packard software.

Analytical method

Doxorubicin and doxorubicinol. Concentrations of doxorubicin and its major metabolite doxorubicinol were determined in all samples by HPLC. Briefly, samples were prepared by adding 1 ml 0.15 *M* sodium borate buffer (pH 9.3) and 100 ng daunorubicin as an internal standard to 1-ml plasma sample and extracting with 8 ml chloroform/isopropanol (4:1, v/v). The organic layer was evaporated to dryness under nitrogen. The residue was reconstituted in 100 μl methanol and 40 μl was injected onto the chromatograph. Plasma concentrations of doxorubicin and doxorubicinol were calculated using the peak area ratios of the two anthracyclines with respect to the internal standard. These were compared with standard curves simultaneously prepared (10 to 100 ng/ml and 5 to 50 ng/ml for doxorubicin and doxorubicinol, respectively). The global intermediate precision was 10.3% for doxorubicin (at 10, 50 and 100 ng/ml concentration levels) and 12.4% for doxorubicinol (at 5, 25 and 50 ng/ml concentration levels), expressed as relative standard deviation (RSD%). Mean recovery at the same concentration levels was 102% and 101% for doxorubicin and doxorubicinol, respectively.

Paclitaxel. Quantitative determination of paclitaxel in plasma was performed using a previously described method [12] modified as follows. Samples (0.550 ml) were buffered with the same volume of 0.2 *M* ammonium acetate (pH 5.0), and 250 ng methylpaclitaxel (internal standard) was added. Paclitaxel and methylpaclitaxel were extracted by loading 1 ml of this mixture onto 1-ml cyano Bond Elut columns (Varian, Bond Elut HF, CN-U, 1 ml/50 mg). Columns were washed with 3 ml deionized water and 1 ml *n*-hexane. After drying under vacuum for 1 min, paclitaxel was eluted using two 1-ml volumes of 0.1% triethylamine in acetonitrile. Final eluents were evaporated to dryness and 50 μl of each reconstituted residue in 100 μl mobile phase was injected onto the chromatograph. A calibration curve using plasma standards of paclitaxel (10 to 1000 ng/ml) were simultaneously processed. The global intermediate precision and recovery were 6.53 RSD% and 99.7%, respectively.

Blank plasma samples from each patient and for each cycle were also analyzed by both methods (doxorubicin/doxorubicinol and paclitaxel) in order to ensure absence of interference.

Pharmacokinetic calculations

The terminal apparent first-order elimination rate constant (β) was estimated from the linear fit of the terminal concentrations. The

area under the concentration vs time curve (AUC) was calculated by the trapezoidal rule from time 0 to the last measured time-point and then by first-order extrapolation to infinite time using the experimentally determined β value for each drug. Clearance (Cl) and volume of distribution (V_{area}) were calculated using noncompartmental methods:

$$Cl = \frac{Dose}{AUC} \qquad Varea = \frac{Dose}{\beta AUC}$$

Statistical analysis

The pharmacokinetic study design allowed within-patient comparison of pharmacokinetic results in different cycles. Thus, the paired *t*-test was applied to evaluate the statistical significance of differences in the results. Student's *t*-test for unpaired data was applied where indicated. The Wilcoxon test statistic was also used to compare the average doxorubicin, doxorubicinol and paclitaxel AUCs measured in cycles 1 and 2 of patients with an absolute LVEF decrease above or below 15% during the administration of the four cycles of neoadjuvant chemotherapy. The statistical significance of the absolute decrease in LVEF during the administration of the four cycles of neoadjuvant chemotherapy was accessed by the sign test statistic, testing zero variation as the null hypothesis. The level of statistical significance was two sided and defined as $P < 0.05$.

Results

Clinical results

Between March 1997 and November 1998, 28 patients with locally advanced breast cancer were included. Their median age was 54 years (range 36–60 years). Of the 28 patients, 3 had stage IIB, 9 stage IIIA and 16 stage IIIB disease. The median number of administered cycles per patient was five (range two to six) with a median interval between cycles of 22.5 days. The average delivered dose intensity of doxorubicin was 18.9 mg/m^2 per week and of paclitaxel was 62.9 mg/m^2 per week.

In two patients the postoperative chemotherapy regimen was changed due to absence of objective response (one patient) or disease progression (one patient). One patient was withdrawn from the study in complete clinical remission after two cycles of doxorubicin-paclitaxel because of grade 3 peripheral neuropathy. One patient received only five of the six planned chemotherapy cycles due to development of a post-mastectomy chest wall abscess after the fifth chemotherapy cycle which took several weeks to resolve.

While grade 3 and 4 neutropenia were frequent (34% and 37% of cycles, respectively), febrile neutropenia occurred in only 6% of cycles, and only three cycles were delayed because of neutropenia on day 21. Except for alopecia and grade 3 peripheral neuropathy in one patient, no other grade 3 or 4 toxicities were observed. There were no dose reductions of doxorubicin or paclitaxel.

After a median cumulative doxorubicin dose of 300 mg/m^2 and a median follow-up of 24 months (range 14 to 35 months), no immediate or delayed clinical cardiac toxicity was observed. The median absolute decrease in LVEF during the four preoperative cycles of chemotherapy was 9% (range 2–27%, $P < 0.0001$). At baseline the median LVEF was 68% (range 60–76%), after a cumulative dose of 360 mg/m^2 of doxorubicin it was 62% (range 55–69%) and after chest wall radiotherapy it was 60% (range 51–68%). However, after a cumulative dose of 240 mg/m^2 of doxorubicin, five patients had an absolute decrease in LVEF of at least 15% (four patients) or to less than 50% (two patients); none of them had known risk factors for cardiac disease. In the two patients with an LVEF drop to below 50%, follow-up MUGA scans performed 3 to 6 months after the end of radiation therapy showed that the LVEF had recovered from 36% to 53% and from 47% to 53%, respectively. There was no relationship between changes in LVEF and the AUC of doxorubicin, doxorubicinol or paclitaxel, chosen as the estimate of systemic exposure to these drugs.

The overall response rate was 86% with three clinical and mammographic complete responses (11%) but no pathological complete responses. No patients had disease progression while on preoperative chemotherapy. After a median follow-up of 24 months (range 14 to 35 months), nine patients had disease recurrence and five of them had died at the time of writing. Another patient died of acute myeloid leukemia without evidence of breast cancer.

Pharmacokinetic results

Comparison of the estimates of doxorubicin, doxorubicinol and paclitaxel pharmacokinetic parameters in either sequence of administration (scheme A→ scheme B and B→A) showed no significant effect of order of cycle administration on the pharmacokinetics of any of the drugs (data not shown). Thus, pharmacokinetic data from all cycles (A or B) were analyzed together regardless of sequence of administration.

The pharmacokinetics of paclitaxel were not dependent upon the time between doxorubicin and paclitaxel administration (Table 1). In contrast, the pharmacokinetics of the anthracyclines were changed by paclitaxel administration. The AUC_{0-24h} of doxorubicin and doxorubicinol were 30% and 80% higher, respectively, in scheme A compared to scheme B ($P = 5.2\times10^{-5}$ and $P = 1.6\times10^{-10}$, respectively). Similarly, doxorubicin and doxorubicinol plasma concentrations 3 h after the anthracycline administration (C_{3h}) were 61% and 132% higher in scheme A than in scheme B ($P = 1.5\times10^{-5}$ and $P = 2.2\times10^{-6}$, respectively). While the administration of paclitaxel increased doxorubicin and doxorubicinol plasma concentrations in both scheme A and scheme B, this was more evident when the plasma level of both drugs was higher, that is, during day 1 of scheme A (Fig. 1).

Possibly due to the lower plasma concentration of the anthracyclines on day 2, only doxorubicinol AUC_{24-48h} was higher in scheme B than in scheme A, despite an

Table 1 Doxorubicin, doxorubicinol and paclitaxel pharmacokinetic parameters measured in scheme A and scheme B (30 min and 24 h between doxorubicin and paclitaxel administration, respectively). Values are means (SD)

Parameter	Doxorubicin			Doxorubicinol			Paclitaxel[a]		
	Scheme A	Scheme B	*P*-value	Scheme A	Scheme B	*P*-value	Scheme A	Scheme B	*P*-value
AUC_{0-24h} ($\mu g/l \cdot h^{-1}$)	684.7 (222.2)	525.0 (139.7)	< 0.001	808.8 (232.8)	449.8 (115.0)	< 0.001	21947 (3775)	19322 (10069)	0.4
AUC_{24-48h} ($\mu g/l \cdot h^{-1}$)	288.9 (101.5)	290.9 (107.8)	0.9	375.1 (103.7)	466.3 (140.9)	< 0.001	1443 (248)	1261 (337)	0.09
AUC_{0-48h} ($\mu g/l \cdot h^{-1}$)	973.5 (308.3)	815.8 (222.9)	< 0.01	1184 (323.9)	916.1 (231.0)	< 0.001	23390 (3897)	20583 (10286)	0.3
C_{3h} ($\mu g/l$)[a]	66.0 (18.7)	40.9 (13.6)	< 0.001	74.5 (23.1)	32.1 (10.4)	< 0.001	–	–	–
$AUC_{0-\infty}$ ($\mu g/l \cdot h^{-1}$)	1397 (732)	1187 (469)	0.2	1759 (543)	1379 (463)	< 0.01	24857 (3776)	22410 (9935)	0.4
Clearance ($l/h/m^2$)	50.7 (19.2)	57.5 (20.7)	0.2	–	–	–	8.21 (1.21)	10.3 (4.03)	0.08
Elimination half-life (h)	38.6 (33.8)	35.2 (19.5)	0.7	33.2 (26.0)	27.4 (14.5)	0.3	27.1 (15.1)	26.0 (8.99)	0.8
V_{area} (l/m^2)	2292 (958)	2548 (995)	0.3	–	–	–	320 (162)	399 (228)	0.5

[a]Based on data collected from the last 12 patients only

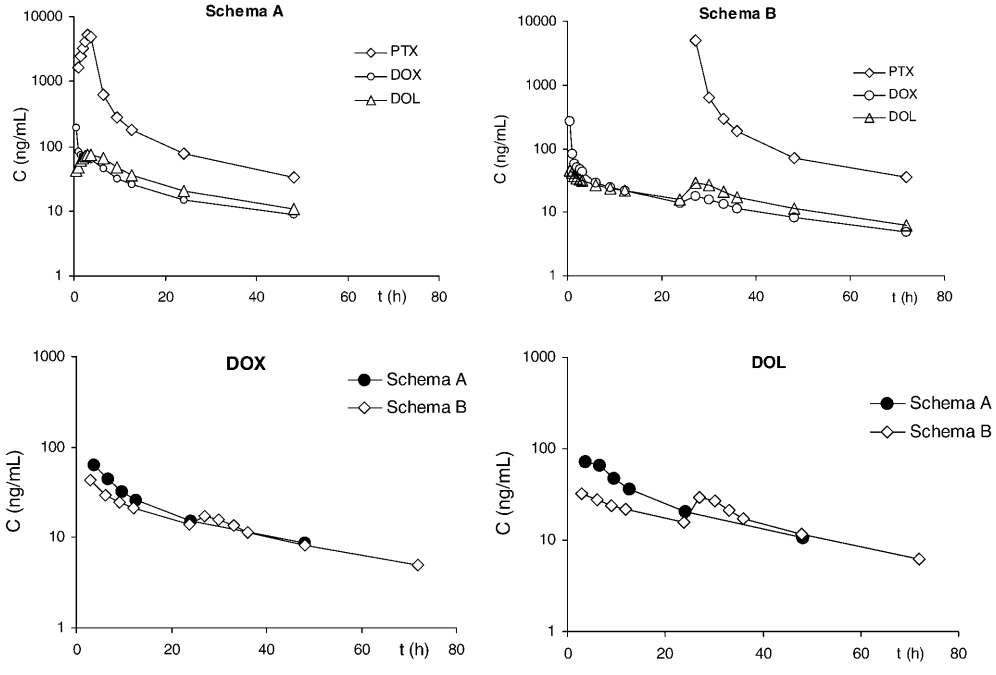

Fig. 1 Plasma concentration versus time profiles of doxorubicin (*DOX*), doxorubicinol (*DOL*) and paclitaxel (*PTX*). Paclitaxel infusion was started 30 min (scheme A) or 24 h (scheme B) after doxorubicin administration

easily recognized rebound increase in doxorubicin and doxorubicinol plasma concentrations seen in all patients after paclitaxel administration on the second day of scheme B (Table 1). The slightly higher AUC of doxorubicinol during the second day of scheme B (after paclitaxel administration) did not compensate for the much higher value of the doxorubicinol AUC observed during the first day of scheme A (in which paclitaxel was administered 30 min after doxorubicin). Thus, there was a statistically significant increase in doxorubicin and doxorubicinol AUCs from time 0 to 48 h in scheme A compared to the AUCs in scheme B. There were no statistically significant differences between scheme A and scheme B in terms of other estimates of anthracycline pharmacokinetic parameters including elimination half-life ($t_{1/2}\beta$), plasma clearance (Clp) and volume of distribution (V_{area}) (Table 1).

The results of the pharmacokinetic analysis performed in the last 12 patients (who had more extensive sample collection) were similar to those of the whole group, except for the difference in doxorubicin AUC and clearance between scheme A and scheme B. In this subgroup, doxorubicin $AUC_{0-\infty}$ was higher (1575 vs 1327 $ng/l \cdot h^{-1}$, $P = 0.01$) and the clearance lower (68.9 vs 81.1 l/h per m^2, $P = 0.03$) in scheme A than in scheme B (30-min and 24-h intervals, respectively).

Discussion

The association of bolus doxorubicin followed immediately by a 3-h infusion of paclitaxel has high antitumor activity but a high risk of cardiac toxicity [4, 5, 7]. To elucidate further the etiology of this cardiac toxicity, we studied in the same 28 patients the pharmacokinetics of doxorubicin and paclitaxel administered at an interval of 30 min (scheme A) or 24 h (scheme B). Each patient acted as her own control, reducing the interpatient variability of the estimates of the pharmacokinetic parameters, and the order of administration of the two chemotherapy schedules was randomly determined to minimize carry-over effects. The pharmacokinetics of paclitaxel were not dependent upon the interval between the administration of doxorubicin and paclitaxel. In contrast, we observed that paclitaxel interfered with doxorubicin pharmacokinetics, increasing the plasma concentration of both doxorubicin and doxorubicinol.

Others have previously reported that the administration of paclitaxel before doxorubicin results in a higher AUC of the anthracycline compared with the opposite sequence of administration [6, 8]. In one study the administration of paclitaxel (over 3 h) 15 min before bolus doxorubicin lead to a higher doxorubicin AUC but lower doxorubicinol AUC in comparison with the reverse sequence of administration, suggesting that paclitaxel interferes with the conversion of the parent compound into its metabolite [6]. In contrast, similar to our findings, the same investigators reported in eight patients that the administration of paclitaxel 24 h after bolus doxorubicin results in a rebound increase of both doxorubicin and doxorubicinol plasma concentrations [6], compatible with paclitaxel interference with or competition for biliary excretion of anthracyclines. Similarly, the concomitant administration of doxorubicin and Cremophor results in an increase in the serum concentration of doxorubicin and doxorubicinol both in mice and in humans [9, 11]. An increase in doxorubicin concentration in cardiac tissue has also been observed in mice treated with doxorubicin and either paclitaxel or Cremophor, suggesting a potential mechanism for the cardiac toxicity [3].

Increased cardiac accumulation of doxorubicin and doxorubicinol has been shown in mdr 1^{a}(–/–) knockout mice treated with doxorubicin, supporting a role for P-glycoprotein blockade in cardiac toxicity [10]. Since bile canaliculi express high concentration of P-glycoprotein and since doxorubicin, doxorubicinol, paclitaxel and Cremophor are all substrates for this transporter, it is possible that paclitaxel alone or with Cremophor may interfere with the biliary excretion of the anthracyclines. In fact, Gianni et al. have demonstrated in vitro that the intracellular retention of doxorubicin in *mdr*-overexpressing breast cancer cells significantly increases with concomitant exposure to paclitaxel and Cremophor [6].

As the cardiac toxicity of anthracyclines is more dependent on high peak plasma concentrations than on overall exposure [2], the observed increase in doxorubicin and doxorubicinol plasma concentrations when paclitaxel was administered 30 min (and not 24 h) after the anthracycline may contribute to the increased cardiac toxicity observed with this schedule of administration.

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