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Docetaxel in combination with epirubicin in metastatic breast cancer: pharmacokinetic interactions

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Abstract

Epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2) were administered to 16 patients affected by metastatic breast cancer following two different schedules: (1) docetaxel as infusion administered 1 h after epirubicin administration (schedule A); and (2) docetaxel as infusion immediately (10 min) after the end of epirubicin i.v. bolus administration (schedule B). Experimental non-compartmental analyses such as AUC and Css, were affected very little by the drug combination, irrespective of whether the administration of docetaxel was immediately after the epirubicin bolus (10 min) or delayed (1 h). However, serum levels showed evidence of transient drug interaction: in schedule A, docetaxel infusion was associated with a transient increase of plasma epirubicin in correspondence with Css_{max} of docetaxel. Bi-compartmental analysis showed a significant difference in epirubicin clearance between protocols A and B. It is suggested that polysorbate 80, used in minimal amounts to formulate docetaxel, may interfere with epirubicin plasma level.

Keywords: Docetaxel; Epirubicin; Pharmacokinetics; Breast cancer

1. Introduction

Docetaxel (Taxotere®) is an analogue of paclitaxel (Taxol®), obtained by semisynthesis from 10-deacetylbaccatin III, extracted from the needles of the European Yew Tree *Taxus baccata* [1,2]. Like paclitaxel, docetaxel exerts its cytotoxic properties by inhibiting microtubule depolymerization and promoting tubulin assembly [3,4]. Docetaxel has shown excellent anti-tumor activity, in both in vitro and in vivo models, and has generally been found to be more active than paclitaxel [5–7]. Docetaxel was first administered to cancer patients in 1990 and clinical phase II studies started in 1992.

Docetaxel has proved very active as a second- and first-line treatment for metastatic breast cancer [8–11]. In addition to breast cancer, docetaxel is also very effective in lung cancer (NSCLC type), achieving a response rate of 38%, which is greater than the maximum response rate expected with other single agents in current clinical use [12–14]. Phase II studies of treatment with docetaxel in ovarian cancer in patients refractory to cisplatin therapy have also yielded satisfactory results (response rates of 41 and 35%) [15,16]. Moreover, in a phase II study, docetaxel has demonstrated various degrees of activity in melanoma, head and neck cancers, gastric cancer, urothelial cancer, soft tissue sarcoma, pancreatic cancer and small cell lung cancer [2].

Paclitaxel is very insoluble in water, and for this reason it has been formulated using Cremophor EL, a toxic substance responsible for serious hypersensitivity reactions [17,18]. High rates of hypersensitivity reactions have also occurred in patients using docetaxel solubilized in a less toxic polysorbate 80 formulation [19]. Myelosuppression, fluid retention, skin toxicity and peripheral neurotoxicity have also been found in docetaxel-treated patients [2], although some side effects may be reduced by prophylactic treatment with corticosteroids or H_1 and H_2 histamine antagonists [20]. At doses > 70 mg/m^2, the pharmacokinetics of doc-

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etaxel is consistent with a three-compartment model. At doses < 70 mg/m^2, a two compartment model has been observed, since the assay used to detect docetaxel was insufficiently sensitive to measure the terminal half life at such low dose [1,21–24]. Like paclitaxel, docetaxel binds to plasma proteins to a great extent ($> 90\%$) and tissue distribution is extensive. Fecal excretion accounts for 70–80% of total drug disposition, whereas renal excretion accounts for $< 10\%$.

The initial metabolite of docetaxel in liver is produced by the hydroxylation of a methyl of the *tert*-butyl group at the C-13 side chain [25]. Kinetic measurements and chemical and immunological inhibition studies have shown that the cytochrome P-450 isoenzyme CYP3A was implicated [26].

By examining the possible in vitro interaction between docetaxel and certain drugs, it was found that cisplatin, verapamil, doxorubicin, vinblastine and vincristine at therapeutic concentrations did not, in general, strongly modify docetaxel metabolism. Combination therapy of docetaxel with other antineoplastic drugs has been found to be very effective in patients with metastatic breast cancer [27,28]. Doses of 50–75 mg/m^2 docetaxel plus 40–50 mg/m^2 doxorubicin administered every 3 weeks as first-line chemotherapy in patients with metastatic breast cancer gave an overall remission (complete plus partial) of 71–81% [29]. Similar results were obtained for a paclitaxel–doxorubicin combination [30]. Preclinical evaluation of paclitaxel pharmacokinetics has demonstrated linearity within the range of pharmacological doses [31]. Non-linearity was observed at the highest dose tested, which was also associated with significant toxicity [32].

Paclitaxel, clinically formulated in Cremophor EL, when administered as the first drug in combination therapy with doxorubicin, significantly increased the peak concentration of doxorubicin compared with the reverse sequence [33]. On the contrary, when doxorubicin was injected 15 min before paclitaxel, longer $t_{1/2}$ beta and higher AUC were observed. This difference became evident when paclitaxel and its 6-hydroxy metabolite reached the highest plasma concentration 1.5 h after the infusion. By starting infusion of paclitaxel (150 mg/m^2) 24 h after the bolus dose of doxorubicin (60 mg/m^2), an increase of doxorubicin concentration persisting for 6 h was evident. Paclitaxel was found to have a marked effect on doxorubicin plasma levels, when the interval between administration of the two drugs was kept to 15 min [31]. These data indicate that paclitaxel caused non-linear distribution and elimination of doxorubicin and that this effect was dose-dependent. When the effects of sequence on tolerability of the combination doxorubicin plus paclitaxel were investigated, it was found that paclitaxel followed by doxorubicin was more toxic than the opposite sequence [32]. Thus, even minor modifications of dose or infusion schedules may have pharmacokinetic or pharmacodynamic sequences [33].

The use of docetaxel in combination with epirubicin (Fig. 1) in the treatment of advanced breast cancer could be a safe and favorable alternative to the paclitaxel–doxorubicin association, which could sometimes entail a risk of congestive heart failure. In a clinical trial I, 75 mg/m^2 docetaxel plus 90 mg/m^2 epirubicin, side effects like fluid retention and cardiotoxicity were not seen, whereas neutropenia was the dose-limiting toxicity [34]. In a phase I/II study of paclitaxel (90 mg/m^2) infused over 3 h, plus epirubicin (200 mg/m^2), it was seen that the pharmacokinetics of paclitaxel was not modified by the administration of epirubicin; on the contrary the metabolism of epirubicin was effected, with a reduction of epirubicinol levels as the paclitaxel dose increased [35].

These findings justify further evaluation of the risks of pharmacokinetic interaction between docetaxel and epirubicin administered in patients affected by metastatic breast cancer. Since these interactions could increase by increasing the interval between the administration of the two drugs, in the present study we compared the possible variations of the pharmacokinetic parameters by administering epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2) and following two different schedules: (1) docetaxel administered 1 h after epirubicin administration (schedule A); and (2) doc-

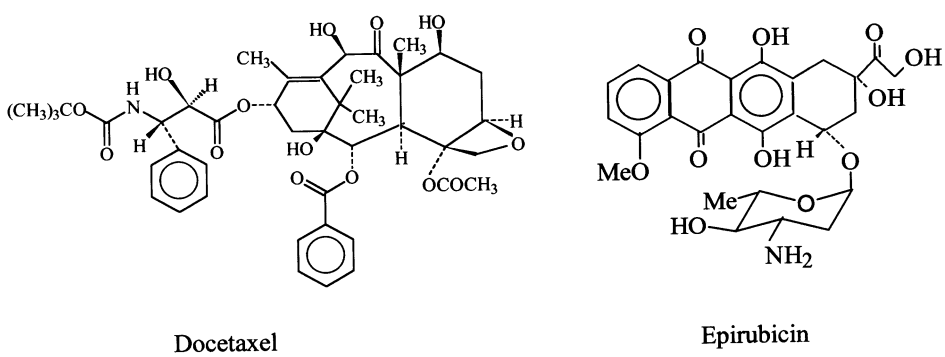

Fig. 1. Structures of docetaxel and epirubicin.

etaxel as infusion immediately after the end of epirubicin administration (10 min) (schedule B).

2. Experimental

2.1. Materials

Epirubicin (Farmorubicina®) was purchased from Pharmacia (Milan, Italy) as 25-ml vials containing 50 mg of drug in 0.9% saline solution. Docetaxel (Taxotere®) was supplied by Rhône Poulenc Rorer (Antony, France) as a concentrated sterile solution that contained 40 mg/ml in a 2-ml vial in polysorbate 80 (Tween 80). The appropriate amount of the drug to be administered to the patient was diluted in 5% dextrose solution, so that the maximum docetaxel concentration was 1 mg/ml. Docetaxel pure powder was supplied by Rhône Poulenc Rorer in a vial containing 100 mg of drug. Pure epirubicin was a gift from Upjohn & Pharmacia (Milan, Italy). Acetonitrile and methanol were purchased from Sigma Aldrich (Milan, Italy). Phosphoric acid and KH_2PO_4 were purchased from Bracco Merck (Milan, Italy). Laboratory grade distilled water was purified with removal of residual ions and organic impurities with a Milli-Q water purification system (Millipore S.A., Molsheim, France) and was filtered through a 0.25 μm membrane filter. Solid-phase extractions were executed with Sep-Pak C18 3 cc (200 mg) and tC2 1 cc (100 mg) cartridges (Waters Chromatography, Milford, MA, USA). Plasma extracts were filtered through Millex SLCR (25 mm, 0.5 μm) filters (Millipore). The HPLC system consisted of a Merck Hitachi L-5000 pump and a Merck Hitachi L-4000 UV spectrophotometer. The analytical column was a stainless-steel tube Symmetry C18 (250×4.6 mm i.d.), with a Symmetry C18 precolumn (Waters). The mobile phase consisted of 60:40 acetonitrile–water (v/v) and was pumped at 1 ml/min. The signal was fed into a Perkin–Elmer LCI-100 integrator.

2.2. Analytical procedures

Two different methods were used to measure plasma concentrations of epirubicin and docetaxel, based on previous procedures reported by other authors [36,37] with some modifications.

2.2.1. Epirubicin analysis and plasma extraction

To 1 ml plasma samples, 1 ml 10 mM phosphate buffer (pH 8) and 1 ml methanol were added. After vortex-mixing and centrifugation at $1000 \times g$ for 10 min, the supernatant was filtered through a Sep-Pak C18 cartridge, previously washed with methanol (3 ml) and 10 mM 67:33 phosphate buffer–methanol (v/v, 3 ml). The cartridge was eluted first with 4 ml 75:25 water–methanol (v/v, discharged), then with 3 ml 0.03 M phosphoric acid in methanol. The elution solvent, after the addition of 10 μl 0.2 M KH_2PO_4, was evaporated to 0.5–1 ml under a nitrogen stream at 25°C. The residue was measured, filtered through Millex SLCR filters, 1:1, diluted with the HPLC mobile phase, and then analyzed by HPLC (200 μl injections).

2.2.2. Epirubicin chromatographic analysis

Epirubicin was determined using a UV detector at a fixed wavelength of 232 nm. The mobile phase was filtered through a 0.5 μm filter (Millipore) and consisted of 75% 10 mM KH_2PO_4 and 25% acetonitrile, adjusted to pH 4.3 with 0.03 M phosphoric acid. This composition was sometimes slightly adjusted (pH and/or percentage of organic modifier) to compensate for variations in column efficiency. The flow rate was 1 ml/min, and epirubicin retention time, in these chromatographic conditions, was about 15 min. The recovery was 58% at 30 ng/ml and 57% at 3000 ng/ml. The inter-assay coefficient of variation was 19% at 30 ng/ml and 9% at 3000 ng/ml. Blank plasma from each patient and each cycle was also analyzed and in no case interfered with detection. The calibration graph was determined by unweighted least-squares linear regression of peak height versus concentration.

2.2.3. Docetaxel analysis and plasma extraction

The extraction cartridges were first activated with 1 ml methanol and 1 ml water. To 0.5 ml plasma samples, 0.5 ml of 70:30 water–acetonitrile (v/v), were added. After vortex-mixing, the sample was transferred to the reservoir of the tC_2 cartridge and filtered. After successive washings with 1 ml of water and 1 ml of 50:50 methanol–water (v/v) elution of docetaxel was performed with 1 ml 67:33 methanol–0.3% phosphoric acid (v/v). This solution was filtered through Millex SLCR filters and 200 μl was injected into the HPLC column.

2.2.4. Docetaxel chromatographic analysis

Docetaxel was determined using a UV detector at a fixed wavelength of 229 nm. The mobile phase was filtered through a 0.5 μm filter (Millipore) and consisted of 60% acetonitrile and 40% water. The flow rate was 1 ml/min and docetaxel retention time, in these chromatographic conditions, was about 6 min. The recovery was 82% at 20 ng/ml and 72% at 2000 ng/ml. The inter-assay coefficient of variation was 7% at 20 ng/ml and 10% at 2000 ng/ml. Blank plasma from each patient and each cycle was also analyzed and in no case interfered with detection. The calibration graph was determined by unweighted least-squares linear regression of peak height versus concentration.

3. Patients and treatment plan

Patients with histologically confirmed breast cancer and metastatic disease were eligible for the study. Other eligibility criteria included: being under 70 years of age; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; and no evidence of major alterations of hepatic, renal or cardiac function at the time of the study. Prior adjuvant therapy was allowed, if stopped at least 6 months before study entry. Adjuvant anthracycline-based therapy was allowed if the total cumulative dose was less than 180 or 360 mg/m^2, in the case of doxorubicin or epirubicin, respectively. Patients must have received no prior chemotherapy for metastatic disease.

Epirubicin (75 mg/m^2) was administered as a 10 min infusion before docetaxel. Docetaxel (75 mg/m^2) was administered as a 1 h infusion. Treatment was given every 3 weeks. Oral steroid medication (8 mg dexamethasone) was given 13, 7 and 1 h before cytotoxic drug administration. Prophylactic steroids were continued on days 1 and 2 (8 mg twice daily).

4. Pharmacokinetic study design

Pharmacokinetic investigations were performed on 16 women receiving epirubicin and docetaxel for metastatic breast cancer. In a group of 11 patients (schedule A) epirubicin was followed by docetaxel after a 1 h interval. In a group of five patients (schedule B), the docetaxel infusion was begun immediately (10 min) after the end of epirubicin administration, to define the effect of the interval between drugs on the disposition of epirubicin and docetaxel.

Blood samples for analysis were obtained at the following times: before epirubicin infusion, at the end of epirubicin bolus, 30 min before the end of docetaxel infusion, at the end of docetaxel infusion, 30 min and 2 h after the end of docetaxel infusion; a further 24 h sample was obtained when possible. Samples of blood (6 ml) were collected in tubes containing potassium edetic acid from a large vein in the other arm than that used for drug infusion. Plasma was separated by centrifugation at $1000 \times g$ for 10 min at 4°C and stored in cap-sealed polypropylene vials at -20°C until analysis. The trial and its pharmacokinetic amendments were approved by the Ethical Committee of the "S. Giovanni Antica Sede" hospital. All patients gave their witnessed informed consent, as required by the Italian law.

5. Results and discussion

The pharmacokinetics of docetaxel and epirubicin was investigated in 16 patients. Table 1 summarizes the main pharmacokinetic parameters obtained from non-compartmental analysis of the two drugs.

AUC and Css for epirubicin were affected very little by the drug's combination with docetaxel, irrespective of whether the administration of docetaxel was immediate or delayed: both maximum plasma concentrations and AUC values were very close. Thus, mean peak plasma concentrations of epirubicin were 2828 ng/ml for schedule A (with a 1 h delayed docetaxel administration) and 2328 ng/ml for schedule B (with epirubicin immediately followed by docetaxel) ($P = 0.5$); similarly, mean AUC values for epirubicin calculated from the concentration–time data were 2456 and 2591 ng/ml per h, for schedules A and B, respectively ($P = 0.8$). There was also no significant difference between schedules for docetaxel parameters, although mean peak plasma concentrations of docetaxel were 1311 and 1865 ng/ml, for schedules A and B, respectively ($P = 0.20$), with a relative increase of 42% (compared with schedule A). Similarly, mean AUC values of docetaxel were 2948 and 4523 ng/ml per h, for schedules A and B, respectively (relative increase of 53%; $P = 0.14$).

Serum levels showed evidence of variable drug interaction: a graphic inspection of the data (Fig. 2) suggested that docetaxel infusion was associated with a rebound in epirubicin disposition only in patients treated with schedule B, while only a small rebound is

Table 1
Non-compartmental pharmacokinetic parameters for epirubicin and docetaxel [a]

Drug	Schedule	Number of patients	Css		AUC	
			ng/ml ± SD	*P*	ng/ml per h ± SD	*P*
Epirubicin	A	11	2828 ± 1572	0.5	2456 ± 1535	0.8
	B	5	2328 ± 1096		2591 ± 1023	
Docetaxel	A	11	1311 ± 604	0.20	2948 ± 1168	0.14
	B	5	1865 ± 426		4523 ± 1501	

[a] AUC was calculated by the trapezoidal rule. *P* was the two-tailed probability level associated with the *t* value in the Student's *t*-test for comparison between schedules A and B.

Table 2
Pharmacokinetics of epirubicin and docetaxel [a]

Pharmacokinetic parameter	Epirubicin schedule A		Epirubicin schedule B		P	Docetaxel schedule A		Docetaxel schedule B		P
	Mean value	DS	Mean value	DS		Mean value	DS	Mean value	DS	
Alpha (h^{-1})	12.95	4.0	20.37	13.66	0.36	7.80	7.62	5.84	1.52	0.46
Beta (h^{-1})	0.17	0.18	0.09	0.02	0.33	0.06	0.02	0.07	0.02	0.76
V_c (l)	13.0	8.3	8.3	4.8	0.29	13.5	8.4	10.0	4.6	0.39
K_{el} (h^{-1})	5.90	3.11	5.26	2.55	0.73	2.83	1.37	3.08	1.66	0.83
$K_{1,2}$ (h^{-1})	6.92	4.04	14.88	11.08	0.25	4.84	7.23	2.69	0.12	0.37
$K_{2,1}$ (h^{-1})	0.30	0.23	0.32	0.14	0.88	0.20	0.18	0.14	0.06	0.42
$t_{1/2}$ alpha (h)	0.06	0.02	0.05	0.04	0.75	0.13	0.06	0.12	0.03	0.83
$t_{1/2}$ beta (h)	10.72	10.71	8.24	2.28	0.61	13.08	8.88	11.11	3.75	0.59
V_{ss} (l)	574.4	821.1	282.9	98.7	0.43	278.5	132.9	218.4	129.2	0.53
$V_{d\beta}$ (l)	816.1	890.5	405.5	155.6	0.32	539.4	278.8	421.9	189.7	0.44
C_l (l/h)	59.56	19.31	35.70	15.15	0.06	30.7	12.7	25.7	2.9	0.28

[a] Compartmental parameters were estimated using the computer program KINETICA™ version 1.1; the concentration versus time curve could be fitted to a bi-exponential decay equation defined as follows: concentration at time $t = A^{-Alpha\ t} + B^{-Beta\ t}$. P is the two-tailed probability level associated with the t value in the Student's t-test for unpaired comparison between patients treated with schedules A and B.

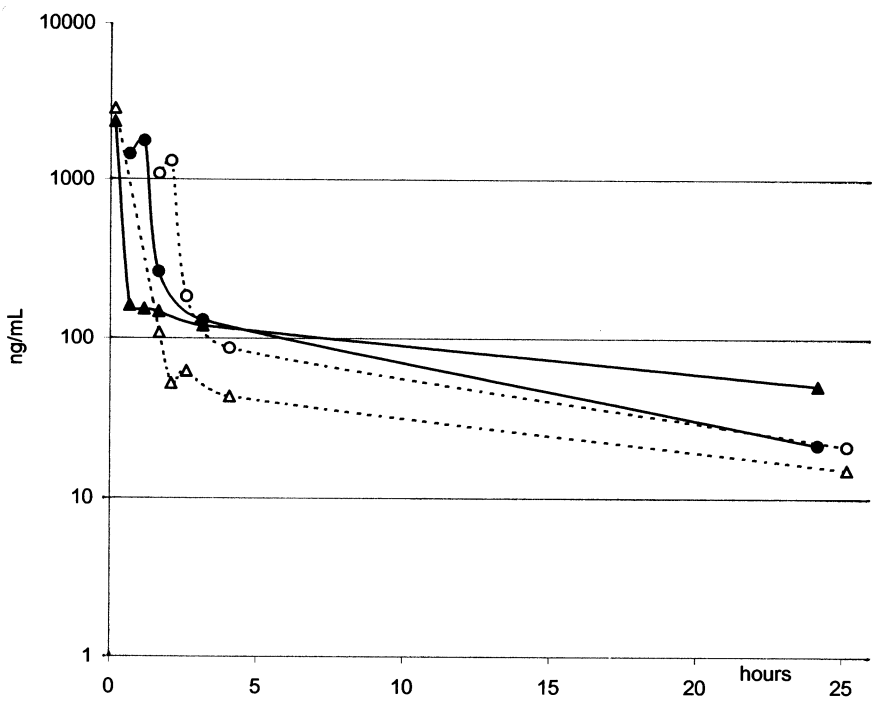

Fig. 2. Effect of interval between drugs on mean plasma disposition of epirubicin and docetaxel. Outline circles and triangles describe the concentration vs. time curve of docetaxel and epirubicin, respectively, in 11 patients treated with schedule A. Values are means ± 50%. Solid circles and triangles describe the concentration vs. time curve of docetaxel and epirubicin, respectively, in five patients treated with schedule B. Values are means ± 50%.

shown in patients treated with schedule A and their mean plasma epirubicin levels in the post infusion phase are higher.

Both epirubicin and docetaxel usually followed a tri-compartmental model [1,21,35]. In our case, tri-compartmental analysis was impossible because of the limited number of samples obtained for the third decay phase of the drugs; thus, bi-compartmental analysis was performed, taking sample points from mean plasma concentrations relative to the first 4 h before the start of infusion of epirubicin, in both schedules A and B.

Pharmacokinetic parameters relative to the α- and β-decay phases are listed in Table 2. There were statistically significant differences in clearance of epirubicin between schedules A and B (Cl A 59.56 l/h versus Cl B 35.70 l/h; $P = 0.06$), whereas no significant difference

could be detected in the volumes (V_c, V_{ss} and $V_{d\beta}$: 13/8.3, 574.4/282.9, 816.1/405.5; $P = 0.29$, 0.43, 0.32) nor in the $K_{1,2}$ and $K_{2,1}$ equilibrium constants. On the other hand, the pharmacokinetic parameters of docetaxel did not seem to vary to a significant extent. Also in this case, the final plasma elimination (in terms of clearance) showed clear but not significant differences in protocols A and B (30.7 l/h in A versus 25.7 l/h in B; $P = 0.28$). Thus, a possible interaction between the two drugs did not effect the distribution, but probably did affect the late elimination phase.

In conclusion, two findings may be extrapolated by varying the interval (from 10 min to 1 h) between i.v. bolus administration of epirubicin and docetaxel infusion:

1. When docetaxel was administered 1 h after epirubicin, a transient increase in the epirubicin plasma level, corresponding to Cp_{max} of docetaxel infusion, was observed. This behavior did not translate into a significant variation of AUC 0–4 h or AUC 0–24 h of docetaxel.
2. A significant increase in epirubicin clearance is seen on moving from schedule A to schedule B. The difference in docetaxel clearance in the two treatment protocols was less evident and statistically not significant.
3. There was no significant variation in either non-compartmental or compartmental parameters for docetaxel in protocols A and B. A certain increase in AUC and Css was observed when docetaxel infusion followed epirubicin administration by 1 h.

The interaction between docetaxel and epirubicin in protocol A, as shown by the transient increase of the plasma level of docetaxel, as well as by the increase in docetaxel clearance, may be due to an interference of docetaxel versus epirubicin, at the level of the late plasma elimination phase and epirubicin biliar excretion. To justify the non-linearity of doxorubicin disposition, it was suggested [31] that a possible interaction between doxorubicin and paclitaxel occurs at the level of a saturable mechanism, such as bile excretion, which is mediated by P-glycoprotein involved in drug resistance [38].

Cremophor EL, present in paclitaxel clinical formulation, is considered to be a modulator of pleiotropic drug resistance [39], as shown by higher drug cell retention when resistant cells are concomitantly exposed to doxorubicin, paclitaxel and Cremophor EL [31]. In our case, docetaxel, clinically formulated in polysorbate 80, did not cause any non-linearity of epirubicin. However, it is possible that some interaction between docetaxel and epirubicin at the excretion level, similar to that suggested [31], may exist. Therefore, it seems possible that polysorbate 80, although to a much lesser extent, may interfere with P-glycoprotein, producing higher epirubicin cell levels; it has recently been shown that Tween 80 is able to reverse multidrug resistance, increasing the epirubicin intracellular level to a much lower extent than Cremophor EL ($1{:}10^4$ versus $1{:}10^3$) [40]. These data are also in agreement with the toxicity shown by epirubicin in Tween 80, such as fluid retention and hypersensitivity reactions [2,19].

These findings imply that reformulation of docetaxel excluding polyethoxylated solubilizing agents may be a future direction of technological research.

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References

[1] B. Fulton, C.M. Spencer, Docetaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of metastatic breast cancer, Drugs 51 (1996) 1075–1092.
[2] E.K. Rowinsky, The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents, Ann. Rev. Med. 48 (1997) 353–374.
[3] S.B. Horwitz, Mechanism of action of taxol, Trends Pharmacol. Sci. 13 (1992) 134–136.
[4] F. Guéritte-Voegelein, D. Guénard, F. Lavelle, M.-T. Le Goff, L. Mangatal, P. Potier, Relationships between the structure of taxol analogues and their antimitotic activity, J. Med. Chem. 34 (1991) 992–998.
[5] M.C. Bissery, D. Guénard, F. Guéritte-Voegelein, F. Lavelle, Experimental antitumor activity of Taxotere (RP 56976, NSC 628503), a taxol analogue, Cancer Res. 51 (1991) 4845–4852.
[6] I. Ringel, S.B. Horwitz, Studies with RP 56976 (Taxotere): a semisynthetic analogue of taxol, J. Natl. Cancer Inst. 83 (1991) 288–291.
[7] A.R. Hanauske, D. Degen, S.G. Hilsenbeck, M.C. Bissery, D.D. Von Hoff, Effects of Taxotere and taxol on in vitro colony formation of freshly explanted human tumor cells, Anti-Cancer Drugs 3 (1992) 121–124.
[8] M.E. Trudeau, E.A. Eisenhauer, B.P. Higgins, F. Letendre, W.S. Lofters, B.D. Norris, T.A. Vandenberg, F. Delorme, A.M. Muldal, Docetaxel in patients with metastatic breast cancer: a phase II study of the National Cancer Institute of Canada — Clinical Trials Group, J. Clin. Oncol. 14 (1996) 422–428.
[9] C.A. Hudis, A.D. Seidman, J.P. Crown, C. Balmaceda, R. Freilich, T.A. Gilewski, T.B. Hakes, V. Currie, D.E. Lebwohl, J. Baselga, G. Raptis, M. Gollub, M. Robles, R. Bruno, L. Norton, Phase II and pharmacologic study of docetaxel as initial chemotherapy for metastatic breast cancer, J. Clin. Oncol. 14 (1996) 58–65.
[10] B. Chevallier, P. Fumoleau, P. Kerbrat, V. Dieras, H. Roche, I. Krakowski, N. Azli, M. Bayssas, M.A. Lentz, M. Van Glabbeke, Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperarative Group of the European Organization for Research and Treatment of Cancer, J. Clin. Oncol. 13 (1995) 314–322.

[11] P. Fumoleau, B. Chevallier, P. Kerbrat, V. Dieras, N. Azli, M. Bayssas, M. Van Glabbeke, Current status of Taxotere (docetaxel) as a new treatment in breast cancer, Breast Cancer Res. Treat. 33 (1995) 39–46.
[12] T. Cerny, S. Kaplan, N. Pavlidis, P. Schoffski, R. Epelbaum, J. van Meeerbeek, J. Wanders, H.R. Franklin, S. Kaye, Docetaxel (Taxotere) is active in non-small-cell lung cancer: a phase II trial of the EORTC Early Clinical Trials Group (ECTG), Br. J. Cancer 70 (1994) 384–387.
[13] J.R. Rigas, Docetaxel in stage III and IV non-small cell lung cancer, Eur. J. Cancer (suppl. 4) 31A (1995) S18–S20.
[14] F.V. Fossella, J.S. Lee, W.K. Murphy, S.M. Lippman, M. Calayag, A. Pang, M. Chasen, D.M. Shin, B. Glisson, S. Benner, Phase II study of docetaxel for recurrent or metastatic non-small-cell lung cancer, J. Clin. Oncol. 12 (1994) 1238–1244.
[15] S.B. Kaye, M. Piccart, M. Aapro, J. Kavanagh, Docetaxel in advanced ovarian cancer: preliminary results from three phase II trials: EORTC Early Clinical Trials Group and Clinical Screening Group, and the MD Anderson Cancer Center, Eur. J. Cancer (suppl. 4) 31A (1995) S14–S17.
[16] P. Francis, J. Schneider, L. Hann, C. Balmaceda, R. Barakat, M. Phillips, T. Hakes, Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer, J. Clin. Oncol. 12 (1994) 2301–2308.
[17] E.K. Rowinsky, R.C. Donehower, Paclitaxel (Taxol), N. Engl. J. Med. 332 (1995) 1004–1014.
[18] A. Sparreboom, O. van Tellingen, W.J. Nooijen, J.H. Beijnen, Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutica vehicle Cremophor EL, Cancer Res. 56 (1996) 2112–2115.
[19] A.T. van Oosterom, D. Schrijvers, Docetaxel (Taxotere®), a review of preclinical and clinical experience. Part. II: clinical experience, Anti-Cancer Drugs 6 (1995) 356–368.
[20] J.E. Cortes, R. Pazdur, Docetaxel, J. Clin. Oncol. 13 (1995) 2643–2655.
[21] R. Pazdur, R.A. Newman, B.M. Newman, A. Fuentes, J. Benvenuto, B. Bready, D. Moore Jr, I. Jaiyesimi, F. Vreeland, M.M. Bayssas, Phase I trial of Taxotere: five-day schedule, J. Natl. Cancer Inst. 84 (1992) 1781–1788.
[22] H.L. McLeod, C.M. Kearns, J.G. Kuhn, R. Bruno, Evaluation of the linearity of docetaxel pharmacokinetics, Cancer Chemother. Pharmacol. 42 (1998) 155–159.
[23] J.-M. Extra, F. Rousseau, R. Bruno, M. Clavel, N. Le Bail, M. Marty, Phase I and pharmacokinetic study of Taxotere (RP 56976, NSC 628503) given as a short intravenous infusion, Cancer Res. 53 (1993) 1037–1042.
[24] R. Bruno, G.J. Sanderink, Pharmacokinetics and metabolism of Taxotere™ (docetaxel), Cancer Surv. 17 (1993) 305–313.
[25] B. Monegier, C. Gaillard, S. Sable, M. Vuilhorgne, Structures of the major human metabolites of docetaxel (RP 56976, Taxotere®), Tetrahedron Lett. 35 (1994) 3715–3718.
[26] I. Royer, B. Monsarrat, M. Sonnier, M. Wright, T. Cresteil, Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs, Cancer Res. 56 (1996) 58–65.
[27] M.J. Piccart, A. Di Leo, Future perspectives of docetaxel (Taxotere) in front-line therapy, Semin. Oncol. (suppl. 10) 24 (4) (1997) S27–S33.
[28] M. Piccart, Docetaxel: a new defence in the management of breast cancer, Anti-Cancer Drugs (suppl. 2) 7 (1996) 9–12.
[29] M. D'Incalci, J. Schüller, T. Colombo, M. Zucchetti, A. Riva, Taxoids in combination with anthracyclines and other agents: pharmacokinetic considerations, Semin. Oncol. (suppl. 13) 25 (6) (1998) 16–20.
[30] J.A. O'Shaughnessy, J.S. Fisherman, K.H. Cowan, Combination paclitaxel (Taxol) and doxorubicin therapy for metastatic breast cancer, Semin. Oncol. (suppl. 8) 21 (5) (1994) 19–23.
[31] L. Gianni, L. Viganò, A. Locatelli, G Capri, A. Giani, E. Tarenzi, G. Bonadonna, Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer, J. Clin. Oncol. 15 (1997) 1906–1915.
[32] L. Gianni, E. Munzone, G Capri, F. Fulfaro, E. Tarenzi, F. Villani, C. Spreafico, A. Laffranchi, A. Caraceni, C. Martini, M. Stefanelli, P. Valagussa, G. Bonadonna, Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastasic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study, J. Clin. Oncol. 13 (1995) 2688–2699.
[33] F.A. Holmes, T. Madden, R.A. Newman, V. Valero, R.L. Theriault, G. Fraschini, R.S. Walters, D.J. Booser, A.U. Buzdar, J. Willey, G.N. Hortobagyi, 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 (1996) 2713–2721.
[34] O. Pagani, Taxoids in combination with epirubicin: the search for improved outcomes in breast cancer, Semin. Oncol. (suppl. 12) 25 (5) (1998) 23–26.
[35] P.F. Conte, E. Baldini, A. Gennari, A. Michelotti, B. Salvadori, C. Tibaldi, R. Danesi, F. Innocenti, A. Gentile, R. Dell'Anna, O. Biadi, M. Mariani, M. Del Tacca, Dose-finding study and pharmacokinetics of epirubicin and paclitaxel over 3 hours: a regimen with high activity and low cardiotoxicity in advanced breast cancer, J. Clin. Oncol. 15 (1997) 2510–2517.
[36] J.C. Vergniol, R. Bruno, G. Montay, A. Frydman, Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method, J. Chromatogr. 582 (1992) 273–278.
[37] C.M. Camaggi, R. Comparsi, E. Strocchi, F. Testoni, B. Angelelli, F. Pannuti, Epirubicin and doxorubicin comparative metabolism and pharmacokinetics, Cancer Chemother. Pharmacol. 21 (1988) 221–228.
[38] M.M. Gottesman, I. Pastan, Biochemistry of multidrug resistance mediated by the multidrug transporter, Annu. Rev. Biochem. 62 (1993) 385–427.
[39] L. Webster, M. Linsenmeyer, M. Millward, C. Morton, J. Bishop, D. Woodcock, Measurement of Cremophor EL following taxol: plasma levels sufficient to reverse drug exclusion mediated by the multidrug-resistant phenotype, J. Natl. Cancer Inst. 85 (1993) 1685–1690.
[40] D.M. Woodcock, M.E. Linsenmeyer, G. Chojnowski, A.B. Kriegler, V. Nink, L.K. Webster, W.H. Sawyer, Reversal of multidrug resistance by surfactants, Br. J. Cancer 66 (1992) 62–68.