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Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy☆

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Abstract

Current dosing strategies for anticancer drugs result in wide interindividual pharmacokinetic variability. Here, we explored the influence of age, body size, concomitant drugs, dose, infusion duration, and sex on the clearance for doxorubicin and docetaxel in 243 individual patients. Patients received doxorubicin ($n=110$) or docetaxel ($n=152$) as monotherapy or in combination chemotherapy regimens. The mean ($\pm$S.D.) clearance was 63.6 ± 22.7 L/h for doxorubicin and 42.8 ± 14.9 L/h for docetaxel. Normalisation for body surface area (BSA) reduced the interindividual variability by only $<1.7\%$. Doxorubicin clearance was significantly reduced when administered at doses >50 mg/m^2 or in combination with cyclophosphamide. Upper extremes of body size were associated with increased clearance for both drugs, whereas no consistent effect of age on clearance was discerned. Overall, these findings suggest that incorporation of variables in addition to BSA should be considered in routine dosing strategies for doxorubicin and docetaxel.

Keywords: Docetaxel; Doxorubicin; Pharmacokinetics; Variability

1. Introduction

There is often a marked variability in drug handling between individual patients, which may contribute to variability in the pharmacodynamic effects of a given drug dose. Hence, an identical drug dose may result in a therapeutic response with acceptable toxicity in one patient, and unacceptable and possibly life-threatening toxicity in another. A combination of physiological, genetic and environmental factors is known to alter the relation between the absolute dose and a drug's concentration-time profile. Over the last few decades, numerous studies have established correlations between systemic exposure to anticancer drugs and drug-induced toxicity or response. These correlations have subsequently been used to individualise chemotherapy regimens either *a priori* or *a posteriori*, for example as in the case of carboplatin and methotrexate, respectively [1,2]. A variety of strategies are now being evaluated to improve the therapeutic index of other anticancer drugs, some of which include implementation of geno- or phenotyping individual patients for drug-metabolising enzymes, the use of biomodulating agents and/or modification of drug scheduling.

Docetaxel and doxorubicin are commonly used for the treatment of a variety of cancers. Although drug-induced toxicity is dose dependent for both of these agents, the individual susceptibility to side-effects varies considerably. As for most other anticancer agents, the

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administered dose of docetaxel and doxorubicin is normalised by a patient's body surface area (BSA). However, for most anticancer agents, clearance is poorly correlated to body-size measures and hence, the routine use of BSA as the only independent variable considered in drug dosing is questionable [3–12]. Previous studies have revealed significant correlations between interindividual variation in docetaxel and doxorubicin clearance and the likelihood of tumour response and/or toxicity [3]. However, the factors contributing to pharmacokinetic variability for these agents are largely unknown and unstudied. In an attempt to further optimise use of these agents, we have now characterised the pharmacokinetics of doxorubicin and docetaxel in a broad patient population under general clinical conditions, and explored demographic subpopulations or drug conditions for which dose adjustment may be needed.

2. Patients and methods

2.1. Patient selection and treatment

All patients studied had a malignant solid tumour and were treated on trials with doxorubicin monotherapy [13], doxorubicin-based combination therapy (with either cyclophosphamide [14], docetaxel [15] or paclitaxel [16]), docetaxel monotherapy [17–21], or docetaxel-based combination therapy (with either capecitabine [18], cisplatin [17], doxorubicin [15], doxorubicin with or without marimastat [22], methotrexate [19], or R101933 [20,21]). Doxorubicin was administered as a bolus (5 min), a short infusion (15–20 min), or as a 1- to 3-h infusion at doses ranging from 40 to 75 mg/m^2, and docetaxel as a 1-h infusion at doses of 55–100 mg/m^2. For the purpose of this study, the drug administration schedule assigned for each agent was based on the coadministered drug and infusion duration (Table 1). Patients were included in these trials if they were over 18 years old and had adequate haematological, hepatic and renal function. Written informed consent was obtained from each patient according to institutional guidelines.

2.2. Pharmacokinetic sampling and analysis

Pharmacokinetic sampling schema and analytical methods employed have been previously described for total drug concentrations [13–24]. All sampling schema involved intensive serial plasma sampling for up to 24-48 h after infusion. Pharmacokinetic studies were performed during one cycle of therapy (cycle 1 or 2). Clearance values for doxorubicin and docetaxel were estimated for individual patients by the method of weighted least-squares regression using either a two- or three-compartment linear model as implemented in *ADAPT II* [25], *WinNonlin* (Pharsight Corp., Mountain View, CA, USA), or *Siphar* (InnaPhase, Philadelphia, PA, USA). Previous investigations evaluating drug exposure-effect relations for doxorubicin and docetaxel have shown that area under the total plasma concentration curve (AUC) is more closely correlated with the principal toxicity (neutropenia) than other pharmacokinetic parameters [26,27]. AUC is a function of both the

Table 1
Drug administration schedules

Drug and administration schedule (infusion duration)	Administration schedule number	Number of patients	No. of Courses	
			Course no. 1	Course no. 2
Doxorubicin				
A 60 mg/m^2 (20 min) followed by CYT 600 mg/m^2 (1 h)	1	19	19	
A 40–60 mg/m^2 (20 min) followed 1 h later by TXT 60–100 mg/m^2 (1 h)	2	22	22	
A 50–75 mg/m^2 (5 min)	3	39	39	
A 60 mg/m^2 (5 min) followed 15 min later by TAX (3 h) 150–200 mg/m^2	4	7	5	2
A 60 mg/m^2 (3 h) coadministered with TAX (3 h) 200 mg/m^2	5	9	9	
A 60 mg/m^2 (5 min) followed 24 h later by TAX (3 h) 150 mg/m^2	6	6	6	
TAX (3h) 200 mg/m^2 followed 15 min later by A 60 mg/m^2 (5 min)	7	8	4	4
Total		110		
Docetaxel				
TXT 60–100 mg/m^2 (1 h)	1	27	27	
A 40–60 mg/m^2 (20 min) followed 1 h later by TXT (1 h) 60–100 mg/m^2	2	19	19	
A 60 mg/m^2 (5 min) followed 1 h later by TXT (1 h) 60 mg/m^2	3	10	10	
TXT 55–100 mg/m^2 (1 h) immediately followed by CIS (3 h) 50–100 mg/m^2	4	57	57	
TXT 75–100 mg/m^2 (1 h) coadministered with oral CAP 825-1250 mg/m^2 twice daily	5	32	32	
TXT 75–85 mg/m^2 (1 h) administered on day 2 with MTX (5 min) 30–50 mg/m^2 administered on day 1 and 15	6	7	7	
Total		152		

CAP, capecitabine; CIS, cisplatin; CYT, cyclophosphamide; TXT, docetaxel; A, doxorubicin; MTX, methotrexate; TAX, paclitaxel.

drug dose and clearance by the equation clearance = dose/AUC; therefore, drug clearance was selected as the parameter for evaluation of pharmacokinetic variability.

Body-size measures, including BSA, lean body mass (LBM), ideal body weight (IBW), adjusted ideal body weight (AIBW) and body mass index (BMI), were calculated as described previously [28–30]. For statistical and graphical analysis, values for BSA were grouped as: lower quartile (25% quantile), interquartile range, and upper quartile (75% quantile). Values for BMI were grouped as: $\leqslant 25$ (normal), 25–29 (overweight), 30–34 (obese), and $\geqslant 35$ (morbidly obese). The four BMI groups were used to display graphically individual clearances; due to the small numbers in the BMI 30–34 and $\geqslant 35$ groups, the data were combined for these two groups for analysis of variance (ANOVA). Values for age were grouped as: <65 years old, 65–69 years old (borderline elderly), and $\geqslant 70$ years old (elderly).

2.3. Statistical analysis

Interindividual differences in clearance were evaluated by the coefficient of variation (CV). The relative reduction in variability (RIV) for clearance was calculated as described previously [9]. Univariate linear-regression analysis was used to assess the relation between body-size indices, age and drug clearance. One-way ANOVA was used to compare the differences in clearance as a function of drug administration schedule (a combination of concomitant drug and infusion duration), categorical age, categorical BSA, categorical BMI and sex, followed by a Tukey–Kramer's multiple-comparison test. Univariate linear least-squares regression analysis and ANOVA were performed using JMP *Statistical Discovery* software, version 4.0.4 (SAS Institute, Cary, NC, USA).

Due to the study design, it was necessary to account for potential confounding variables and the correlation between individuals from the same protocol. Random-effects multiple linear-regression models were used to assess the influence of dose, concomitant drugs, infusion duration, age, sex and BSA (predictor variables) on drug clearance (outcome) where a random effect was included to account for correlation between individuals within an administration schedule. This approach assumes independence between individuals from different protocols, but assumes that outcomes from individuals in the same protocols are correlated. First, the associations between predictor variables were assessed to detect possible multicolinearity in regression models: categorical variables were compared using Fisher's exact test; continuous variables were compared using Pearson and Spearman correlation; categorical variables were compared to continuous variables using ANOVA. This analysis was exploratory in nature and necessary due to the observational nature of the data set. Random-effects models were then fit to the data iteratively and interactions between predictors were also considered. Regression coefficients, standard errors of the coefficients, and the associated *P*-values were determined. The coefficients represent the expected difference in clearance for a one-unit difference in a predictor, adjusted for the other predictors in the linear-regression model. Multiple linear-regression modelling was performed using the software *STATA*, version 7.0 (Stata Corporation, Cary, NC, USA). The *a priori* level of significance was set at $P<0.05$.

3. Results

Patient demographics are summarised in Table 2.

Table 2
Patient details

Patient characteristics	Doxorubicin therapy	Docetaxel therapy
Total number of patients	110[d]	152[d]
Age (years (range))	52.5[a] (27–78)	53.1[a] (21–75)
<65	94[b]	128[b]
65–69	9[b]	16[b]
⩾70	7[b]	8[b]
Sex (male:female)	34:76	69:83
Height (cm (range))	165.9[a,c] (140–193)	170.9[a] (149–193)
Weight (kg (range))	74.1[a,c] (38–117)	73.3[a] (39.3–109.2)
BSA (m^2 (range))	1.83[a,c] (1.26–2.42)	1.86[a] (1.28–2.38)
25% quartile	1.67	1.71
Median	1.78	1.84
75% quartile	1.97	2.00
LBM (kg (range))	53.9[a,c] (34.1–72.3)	54.2[a] (31.8–78.8)
IBW (kg (range))	59.1[a,c] (34.1–87.3)	64.5[a] (42.3–87.3)
AIBW (kg (range))	62.6[a,c] (41.9–86.6)	66.7[a] (41.5–90.6)
BMI (range)	26.6[a,c] (15.5–43.6)	25.1[a] (16.4–40.5)
<25	40[b]	80[b]
25–29	37[b]	50[b]
30–34	15[b]	18[b]
⩾35	7[b]	3[b]
Clearance (L/h)	63.6[a] (16.6–124.5)	42.8[a] (13.8–84.4)
Infusion duration	0.47 (0.07–3)	1.05[a] (0.92–1.50)
Bolus	57[b]	
Short infusion	43[b]	
Long infusion	10[b]	

[a] Results expressed as mean.
[b] Data are the number of patients.
[c] Height, body surface area (BSA), lean body mass (LBM), ideal body weight (IBW), adjusted ideal body weight (AIBW) and body mass index (BMI) were available for 99 of 110 patients; weight was available for 104 of 110 patients.
[d] 19 patients received both doxorubicin and docetaxel in combination therapy and are represented in both data sets; the total number of individual patient studies were 243.

Table 3
Mean (±S.D.) clearance of doxorubicin and docetaxel as a function of body-size measures

Body-size measure	Doxorubicin[a]		Docetaxel	
	% CV	Clearance[b]	% CV	Clearance[b]
None (L/h)	30.8	66.9±20.6	34.8	42.8±14.9
BSA (L/h/m^2)	30.6	37.1±11.3	34.2	23.0±7.9
LBM (L/h/kg)	32.0	1.3±0.4	35.0	0.8±0.3
IBW (L/h/kg)	33.9	1.2±0.4	35.8	0.7±0.2
AIBW (L/h/kg)	32.4	1.1±0.4	35.4	0.7±0.2
BMI (kg/m^2)	33.3	2.6±0.9	36.8	1.7±0.6
Height (L/h/cm)	30.0	0.4±0.1	36.0	0.3±0.1
Weight (L/h/kg)	35.1	0.9±0.3	36.7	0.6±0.2

Abbreviations as in Table 3.
[a] Excludes patients enrolled to drug administration schedule no. 1. $n=91$ for none, $n=86$ for weight, $n=82$ for all others.
[b] Mean±S.D.

3.1. Doxorubicin pharmacokinetics

The mean plasma clearance of doxorubicin in the entire group was 63.6±22.6 L/h (range, 16.6–125 L/h) with a CV of 35.5% (Table 3), similar to previous findings [31]. Compared to the other drug-administration schedules, doxorubicin clearance was reduced by approximately 30% when coadministered with cyclophosphamide (47.9±25.6 L/h versus 66.9±20.6 L/h; $P=0.0007$) (Fig. 1A); consequently, these 19 patients were excluded from subsequent analysis. A positive association was observed between BSA and doxorubicin clearance ($r=0.34$; $P=0.0015$); a separate analysis in males and females revealed a stronger correlation in males ($r=0.64$; $P=0.0002$) than females ($r=0.01$; $P=0.95$). However, when normalised to BSA, the RIV for clearance was 0.8%. Consequently, only for males did normalisation of clearance to BSA result in a substantial reduction in variability of clearance (RIV 18.7%). A trend for increasing doxorubicin clearance as BSA increased from the lower quartile to the upper quartile was observed; clearance was 20% higher in patients with BSA in the upper quartile (BSA > 1.97 m^2) (63.1±22.6 L/h versus 64.7±17.3 L/h versus 76.6±24.2 L/h; $P=0.061$) (Fig. 2A). Similarly, clearance was 22% higher in patients with BMI ⩾30 kg/m^2 (63.6±19.9 L/h versus 65.7±17.1 L/h versus 78.9±27.3 L/h; $P=0.045$) (Fig. 3A). Although doxorubicin clearance was reduced by 13% in females compared to males (63.3±19.2 L/h versus 73.0±22.2 L/h; $P=0.032$), no sex differences were noted when clearance was normalised to BSA (37.0±12.4 L/h/m^2 versus 37.3±9.37 L/h/m^2; $P=0.90$). Age was not associated with reductions in doxorubicin clearance ($P=0.88$) (Fig. 4A); however, the number of patients in the population studied that were aged 65–69 years ($n=4$) or ⩾70 years ($n=6$) may not be adequate to detect a difference if one exists.

Multiple linear regressions helped to determine that concomitant medication and sex, and concomitant medication and infusion duration were strongly confounded. Therefore, concomitant medication was not included in the final multiple linear-regression model. In addition, preliminary modelling indicated that infusion duration was not significantly associated from clearance so it was not included in the final model. Interactions were found between sex and BSA, and sex and dose. As a result, the associations between predictor variables and doxorubicin clearance were stratified by sex, summarised in Table 4. At doxorubicin doses greater than 50 mg/m^2, there was a trend for decreased clearance, although this did not reach a level of significance (coefficient = −10.63; $P=0.056$). Assuming an average clearance of 63 L/h, this would represent a 17% decrease in clearance when doxorubicin is administered at doses >50 mg/m^2. BSA was positively associated with clearance in males (coefficient = 66.42; $P<0.001$) but not in

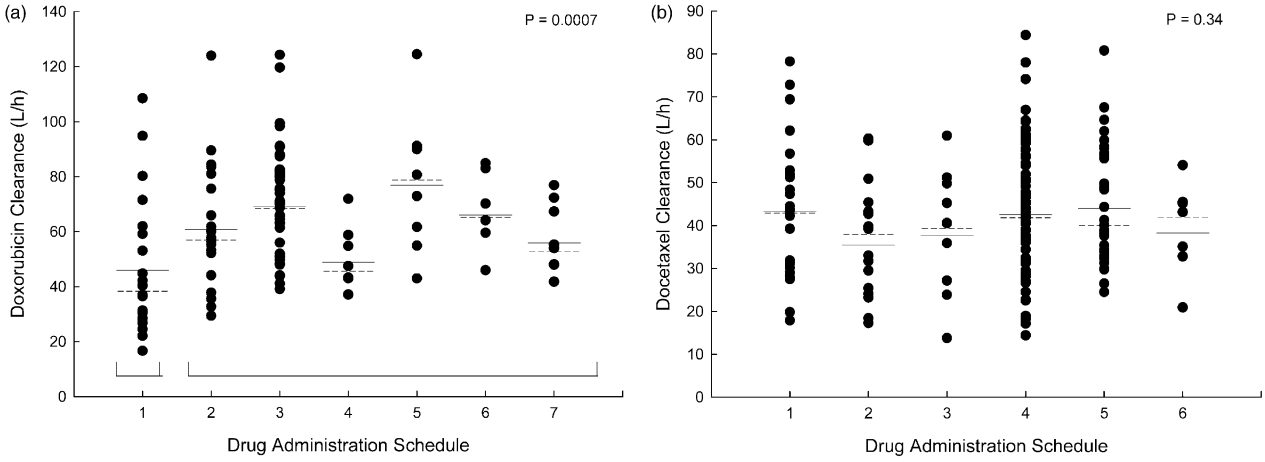

Fig. 1. Clearance as a function of drug administration schedule for (a) doxorubicin and (b) docetaxel. The solid line represents the mean, while the dashed line represents the median.

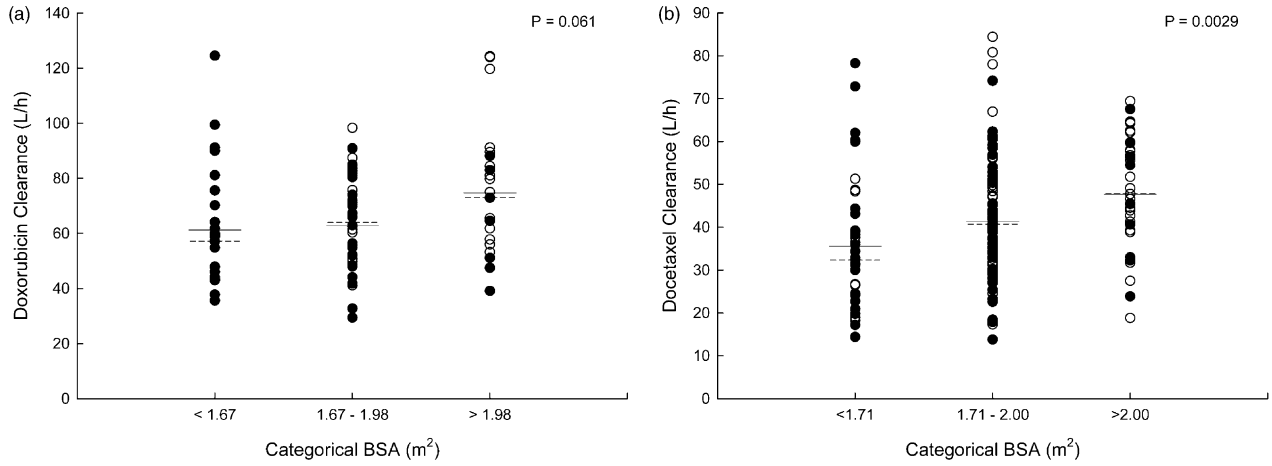

Fig. 2. Clearance as a function of body surface area (BSA) and sex for (a) doxorubicin and (b) docetaxel, where ○ is male and ● is female. The solid line represents the mean, while the dashed line represents the median.

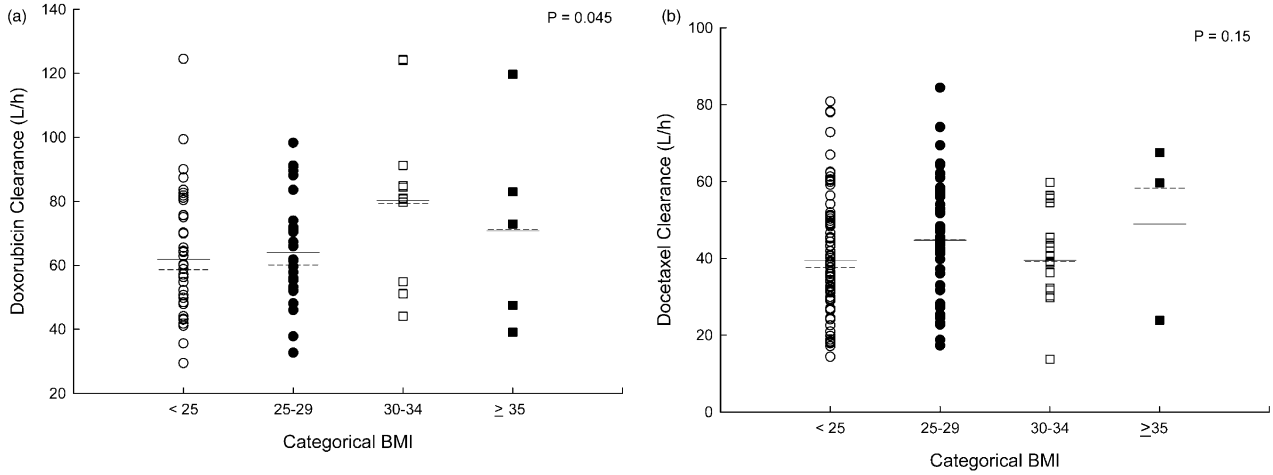

Fig. 3. Clearance as a function of body mass index (BMI) for (a) doxorubicin and (b) docetaxel, where ○ is <25, ● is $\geqslant 25$–29, □ is 30–34, and ■ is $\geqslant 35$. The solid line represents the mean, while the dashed line represents the median.

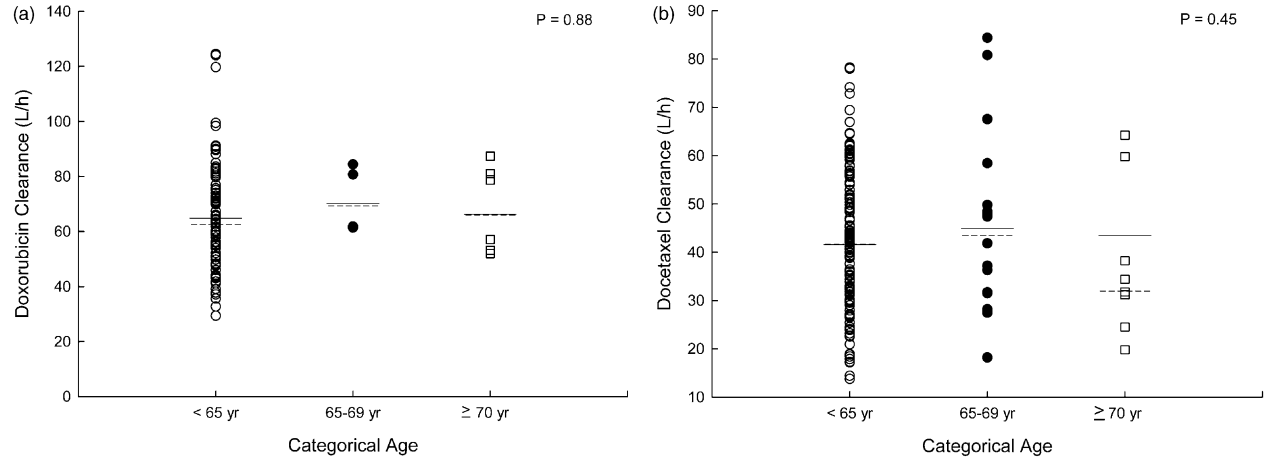

Fig. 4. Clearance as a function of categorical age for (a) doxorubicin and (b) docetaxel, where ○ is <65, ● is $\geqslant 65$ and <70, and □ is $\geqslant 70$ years old. The solid line represents the mean, while the dashed line represents the median.

Table 4
Multiple regression model for doxorubicin clearance

	Coefficient	Standard error	P
Males ($n=29$)			
Intercept	−50.03	26.80	0.11
High dose[a]	−10.63	4.49	0.056
BSA	66.42	9.72	<0.001
Age	−0.05	0.21	0.82
Females ($n=69$)			
Intercept	83.15	31.15	0.04
High dose	−10.63	4.49	0.056
BSA	−7.46	13.84	0.61
Age	−0.05	0.21	0.82

BSA, body surface area.
[a] High dose is binary with a dose greater than 50 mg/m^2 coded as 1, and less than or equal to 50 coded as 0.

females (coefficient = −7.46; $P=0.61$), and age was not associated with altered drug clearance (coefficient = −0.05; $P=0.82$).

3.2. Docetaxel pharmacokinetics

The mean plasma clearance of docetaxel was 42.8±14.9 L/h (range 13.8–84.4 L/h) with a CV of 34.8% (Table 3), and was similar among the different drug-administration schedules ($P=0.34$) (Fig. 1B). A positive correlation was noted between BSA and docetaxel clearance (r = 0.30; $P=0.0002$); a separate analysis revealed a stronger correlation in males (r = 0.35; $P=0.0032$) than in females (r = 0.18; $P=0.11$). After normalisation of clearance for BSA, the mean was 23.0±7.87 L/h/m^2 with an associated CV of 34.2%, indicating a negligible RIV for clearance of 1.7%. However, the mean clearance increased as BSA increased from the lower to the upper quartile, and was significantly higher by 33% in patients with BSA >2.0 m^2 (36.8±15.9 L/h versus 42.6±14.4 L/h versus 49.0±13.0 L/h; $P=0.0029$) (Fig. 2B). Clearance was not higher in patients with BMI ⩾30 kg/m^2 (40.9±15.0 L/h versus 46.1±15.2 L/h versus 42.3±13.3 L/h; $P=0.15$) (Fig. 3B). Docetaxel clearance was reduced on average by 11% in females compared to males (40.6±14.7 L/h versus 45.6±14.8 L/h; $P=0.040$), although no sex differences were noted when clearance was normalised to BSA (22.9±8.44 L/h/m^2 versus 23.2±7.19 L/h/m^2; $P=0.88$). Advanced age was not associated with reduced docetaxel clearance in 16 patients between the ages of 65 and 69 years and 8 patients aged ⩾70 years ($P=0.45$) (Fig. 4B).

Using multiple linear-regression analysis, an interaction between sex and BSA was observed, and therefore results are stratified for males and females. The association between predictor variables and docetaxel clearance is summarised in Table 5. BSA was associated with docetaxel clearance in males only (coefficient = 28.11; $P=0.039$). Concomitant treatment with doxorubicin and capecitabine was associated with decreased and increased docetaxel clearance, respectively (for doxorubicin, coefficient = −8.57; $P=0.014$; for capecitabine, coefficient = 1.48; $P=0.010$). Assuming an average docetaxel clearance of 42.8 L/h, the coefficient of −8.57 indicates that cotreatment with doxorubicin results in a 20% decrease in clearance. No association was observed between age and docetaxel clearance ($P=0.67$).

Table 5
Multiple regression model for docetaxel clearance

	Coefficient	Standard error	P
Males ($n=69$)			
Intercept	4.47	7.54	0.58
Dose[a]	−0.10	0.08	0.27
Age	−0.09	0.19	0.67
Concomitant drug: doxorubicin	−8.57	2.29	0.014
Concomitant drug: cisplatin	0.25	0.43	0.59
Concomitant drug: capecitabine	1.48	0.37	0.010
Concomitant drug: methotrexate	−5.05	2.51	0.10
BSA	28.11	10.08	0.039
Females ($n=83$)			
Intercept	31.44	14.24	0.078
Dose[a]	−0.10	0.08	0.27
Age	−0.09	0.19	0.67
Concomitant drug: doxorubicin	−8.57	2.29	0.014
Concomitant drug: cisplatin	0.25	0.43	0.59
Concomitant drug: capecitabine	1.48	0.37	0.010
Concomitant drug: methotrexate	−5.05	2.51	0.10
BSA	13.23	10.69	0.27

BSA, body surface area.
[a] Dose was included as a continuous variable.

4. Discussion

The traditional method of individualising anticancer drug dosage in adult patients is by using BSA [3–9,32,33]. The usefulness of normalising anticancer drug doses to BSA has been questioned, since it has been shown that for some agents there is no correlation between BSA and anticancer drug clearance [3–12,32,33]. In these cases, the use of BSA-adjusted dosing results in the administration of a standard dose multiplied by an arbitrary number (i.e. the ratio of the patient's BSA to an average BSA). These considerations have led to a desire for better tools to individualise chemotherapy, and to new ways of evaluating and treating patients. In the present study, exploratory relations were assessed between the disposition characteristics of doxorubicin and docetaxel and a number of common patient- and drug-related variables.

Doxorubicin clearance was decreased by approximately 17% at doses >50 mg/m^2, consistent with a previous report suggesting non-linear disposition [34]. In contrast, some investigators have observed the

absence of dose and time dependency, possibly on the basis of sparsity of data sets [35]. It was also observed that doxorubicin clearance was reduced (30%) when coadministered with cyclophosphamide, which is in line with a previous report [36]. This interaction has been attributed to the reduced formation of the doxorubicin 7-deoxyaglycone metabolite, and hence decreased elimination of the parent drug [37]. The administration of doxorubicin doses >50 mg/m^2 when combined with cyclophosphamide could result in greatly reduced doxorubicin clearance. These observations provide mechanistic support for recent observations in a continuing clinical trial in adjuvant breast cancer (NSABP B-30, see: www.nsabp.pitt.edu), where excessive toxicity, including the occurrence of toxic deaths, was noted in the original TAC regimen combining doses of doxorubicin 60 mg/m^2, docetaxel 60 mg/m^2 and cyclophosphamide 600 mg/m^2. However, similar events were not observed in another trial in adjuvant breast cancer that used TAC doses of 50, 50 and 500 mg/m^2 [38]. In contrast to cyclophosphamide, taxanes in the tested schedules had no apparent effect on the clearance of doxorubicin by univariate analysis but could not be tested in multiple linear-regression analysis because of confounding predictor variables. We could therefore not confirm previous observations describing effects of docetaxel or paclitaxel on doxorubicin pharmacokinetics [15,16].

Similar to most other chemotherapeutic agents, in the entire population studied, dose calculations based on BSA did not significantly reduce interpatient variability in doxorubicin clearance. However, doxorubicin clearance was approximately 20% higher in patients with BSA >1.97 m^2 ($P=0.061$) and BMI $\geqslant 30$ kg/m^2 ($P=0.045$). It is noteworthy in this context that a previous study involving 21 patients indicated that drug clearance was reduced by almost 50% in seven obese females, where obesity was defined as greater than 130% of IBW [39]. This observation was not confirmed in the present investigation either for females or males in a broader patient population. Doxorubicin clearance was unaltered in 10 elderly patients, consistent with previous findings in 9 elderly patients [40]. However, another study involving 56 patients, seven of whom were aged $\geqslant 70$ years, showed a linear association between age and clearance, although complete overlap in clearance was observed in patients between the ages of 40 and 80 years [41].

In the case of docetaxel, a multiple regression analysis revealed a 20% decrease in clearance in the presence of doxorubicin. Although the mechanistic basis for this interaction is unknown, it may be clinically significant considering the notion that a 25% decrease in docetaxel clearance significantly increases the odds for development of febrile neutropenia [42,43]. It provides a further explanation for the severe haematological toxicity observed in regimens combining doxorubicin with docetaxel.

Similar to doxorubicin, normalisation of docetaxel clearance to BSA resulted in negligible reduction in variability in clearance. However, also similar to doxorubicin, docetaxel clearance was increased by approximately 33% in patients with BSA >2.0 m^2 ($P=0.0029$); this association was not observed, however, in obese patients with BMI $\geqslant 30$ kg/m^2 ($P=0.15$) despite 15 of 21 patients being identical in the two subcategories. It thus remains unclear if docetaxel clearance is altered in obese patients. It is still debatable whether the interpatient variability of docetaxel clearance has a clinically meaningful correlation with BSA. Although Bruno and colleagues reported that BSA is a significant covariate for docetaxel clearance [43], the only clinically relevant variables that impact significantly upon clearance of this drug are altered levels of transaminases and alkaline phosphatase [42]. Thus, although docetaxel clearance may be weakly related to BSA, this measure does not contribute substantially to explaining interindividual pharmacokinetic variability.

In the present population, docetaxel clearance does not appear to be significantly reduced in elderly patients, which lends further support to a population pharmacokinetic analysis indicating that age is not a significant covariate for clearance [42,43]. In contrast, a previous investigation in a group of 226 patients with equal histopathological conditions has shown a significant decline in the content of the main docetaxel-metabolising enzyme (i.e. cytochrome P450 3A) in patients after 70 years of age [44]. A confirmatory multi-institutional trial that includes phenotyping for cytochrome P450 3A is currently being conducted in patients of different age groups.

Although recent investigations have provided evidence against the use of BSA in anticancer drug dosing [3–12], there may be some situations, in the absence of more accurate and validated dosing strategies, where BSA-based dosing is relevant. For example, the present investigation observed an increase in drug clearance at the upper extremes of body size; for the agents studied, under these circumstances, normalising drug dose to BSA could account for some of the variability in clearance. In addition, the data do not justify the capping of BSA at 2.0 m^2 or using ideal body weight in the formula for BSA when calculating drug dose for obese patients. Alternative weight descriptors for dose adjustment of these anticancer agents in obese patients are being evaluated, as recently described [45].

In conclusion, the current analysis confirms a number of findings previously described by conventional pharmacological analyses in smaller numbers of patients. The current statistical evaluation has also eliminated several candidate covariates from further consideration as important determinants of drug disposition. It is

difficult to make specific recommendations for dosing changes of doxorubicin- or docetaxel-containing chemotherapeutic regimens on the basis of the current findings. Although monitoring of plasma concentrations and dosage adjustment may be necessary to optimise anticancer efficacy in patients, therapeutic drug monitoring is not routinely available for these agents. Regardless, the described data increase our knowledge on these clinically important drugs, and provide the basis for designing future, prospective investigations aimed at evaluating alternative and improved dosing regimens.

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