Cancer Chemother Pharmacol (2011) 67:93–101
DOI 10.1007/s00280-010-1288-y

ORIGINAL ARTICLE

An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity

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Received: 22 October 2009 / Accepted: 12 February 2010 / Published online: 5 March 2010

Abstract
Purpose Although body composition has emerged as an important predictor of drug efficacy and toxicity, explanations for this association are unclear. Our goal was to investigate relationships between lean body mass (LBM), liver size/function and epirubicin pharmacokinetics (PK) and toxicity.
Methods Data from a clinical study ($n = 24$) of patients with breast cancer receiving adjuvant intravenous $FE_{100}C$ chemotherapy were used to examine relationships between LBM, liver size, and epirubicin clearance. Muscle tissue and liver mass were measured by analysis of computerized tomography cross-sectional images, and an extrapolation of muscle mass to total LBM compartment was employed. Population PK analysis of epirubicin was undertaken to test effects of body composition on epirubicin clearance and area under the curve (AUC).
Results Estimated LBM was extremely variable in this cohort ranging from 32.9 to 67.3 kg. LBM was associated with neutrophil nadir ($r = 0.5$, $P = 0.023$), and mean LBM was lower for patients presenting with toxicity compared to those where toxicity was absent (41.6 vs. 56.2 kg, $P = 0.002$); 33% of variance in clearance was explained by LBM and aspartate aminotransferase (AST). Liver mass was fnot related to epirubicin clearance likely due to larger livers presenting with larger fat content, but liver attenuation (degree of fat infiltration) and AST were associated with AUC.
Conclusion To our knowledge, this is the first study to examine relationships between LBM, liver mass/function and epirubicin PK and toxicity. This exploratory work investigates the notion of organs and tissues having distinctive contributions to the distribution and metabolism of antineoplastic drugs.

Keywords Body composition · Lean body mass · Epirubicin · Pharmacokinetics · Clearance · Liver mass · Liver attenuation

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Introduction

Body surface area (BSA) has routinely been used in medical oncology for dosing anti-neoplastic agents in spite of considerable limitations in its accuracy at predicting chemotherapy efficacy and toxicity [1–4]. Baker et al. [5] investigated pharmacokinetic (PK) properties of 33 anti-neopastic agents tested in phase I clinical trials and found that BSA-based dosing reduced interpatient PK variability for only 5 (15%) drugs. Pharmacokinetics provides the scientific basis for dose selection, and its variability among patients reflects complex interactions of several genotypic

and phenotypic factors. Body composition, specifically the body proportions of lean and adipose tissues and organs, is one of the phenotypic factors that may affect metabolism and toxicity of chemotherapy drugs. Each tissue contributes to drug distribution and metabolism according to its mass and its specific rate of uptake and metabolism (participation in the metabolic activation or deactivation of drug). Although this concept has not been systematically investigated, the tissue specificity of uptake and metabolism of a few antineoplastic agents has been described [6–8]. Volume of distribution of relatively hydrophilic drugs correlates well with lean tissue mass or lean body mass (LBM), which includes metabolic tissues such as liver, kidney, muscle and intra/extra-cellular water. Likewise, increased adipose tissue may increase volume of distribution for highly lipophilic drugs prolonging their elimination half-lives [9].

Recent studies confirmed that low LBM is associated with more severe toxicity to the fluoropyrimidines 5-fluorouracil (5FU) and capecitabine [10, 11]. Consequently, patients with low LBM are relatively overdosed and present with higher rates of chemotherapy toxicity. A pharmacokinetic explanation is that these patients have a low volume of distribution and poor drug metabolism/clearance [10].

The liver is responsible for concentrating and metabolizing the majority of chemotherapy agents, which are processed by a variety of soluble and membrane-bound enzymes especially within the hepatocyte endoplasmic reticulum. Each drug has its specific enzyme disposal pathway(s) of biotransformation involving one or more of these enzyme systems. Liver drug metabolism is related to organ size/volume, drug-metabolizing enzyme activity and liver blood flow. Liver is a highly plastic organ and its size and contribution to total body weight are influenced by a variety of factors in patients with cancer [12], including age (decline of liver mass by 20–40% with aging), chronic malnutrition (decline in liver volume by 10–20%), liver disease (i.e., cirrhosis), liver dysfunction (i.e., steatosis), surgical resection and hepatomegaly triggered by infection, inflammation or metastases. Consequently, while the normal liver volume is approximately 1,714 cm^3, variation in liver volume and function represents an important variable in inter-patient chemotherapy drug metabolism.

Epirubicin, an anthracycline cytotoxic agent, is a liver-metabolized drug with poorly understood inter-patient pharmacokinetic (PK) variability. Gurney et al. [13] studied epirubicin PK in patients given a standard dose of epirubicin in proportion to their BSA and found a mean (SD) clearance of 84.6 (63.5) l/h. Camaggi et al. [14] found substantial variation in epirubicin clearance in eight patients with a mean clearance of 75.0 l/h and a range from 35.6 to 133.4 l/h.

As image-based methods of analysis of body composition based on dual energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and computerized tomography (CT) have begun to be applied to patients with cancer [15], a number of recent publications point to considerable variation in the proportions of lean and adipose tissues and organ size in contemporary populations of patients with cancer [10–12, 16]. Lean body mass is reported to vary by 2–3 times [10, 11, 16], while liver volume ranges from 1,904 to 3,619 cm^3 (interquartile range) [12].

In this exploratory investigation, we sought to relate epirubicin PK and toxicity to specific features of body composition of patients with breast cancer, focusing on LBM and functional liver volume.

Methods

Patients and study design

This analysis was done within the context of pharmacogenetic predictors of toxicity to epirubicin chemotherapy in patients with stage II or III breast cancer, a prospective study carried out at the Cross Cancer Institute, Edmonton, AB, Canada, from January 2002 to December 2004. All patients provided informed consent for the original study, which was approved by the Alberta Cancer Board Research Ethics Board. Further analysis of clinical toxicity data and interpretation of body composition from CT images was approved by the same local ethics board.

Women with breast cancer treated with adjuvant $FE_{100}C$ (5FU 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) chemotherapy were eligible for enrollment. BSA was calculated using the Mosteller formula [BSA (m^2) = ([Height (cm) × Weight (kg)]/3,600)$^{1/2}$]. Eligibility criteria included age ≥18 years; no pre-existing liver disease, a serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 times the upper limit of normal (ULN), a total bilirubin ≤ the ULN, and normal cardiac (left ventricular ejection fraction (LVEF) by MUGA ≥50%) and renal function (creatinine ≤1.5 times the ULN). Patients with metastatic disease were excluded. The study was approved by the Alberta Cancer Board Research Ethics Board according to good clinical practice, the declaration of Helsinki and applicable regulations. Informed consent was obtained from all participants. $FE_{100}C$ chemotherapy was given intravenously every 3 weeks [17]. Primary prophylaxis with granulocyte colony-stimulating factor and antibiotics was prohibited. Epirubicin concentrations were drawn at approximately 1 and 24 h after the end of the epirubicin infusion with exact times recorded. Epirubicin was administered as an infusion

with a median duration of 20 min (range 15–75 min). Patients had a complete blood count and differential count done prior to chemotherapy and on days 8 and 15 of cycle one.

Toxicity and efficacy assessment

Toxicity was graded according to the NCI-CTEP Common Toxicity Criteria, version 2.0. Patient toxicity assessments were obtained by a diary provided prior to each cycle of chemotherapy, and this was reviewed in person by a research nurse after each cycle. Toxicity profiles were obtained for all cycles but only first-cycle toxicities were analyzed for this study because patients who had severe toxicity had dose reductions for subsequent cycles. Common toxicities were neutropenia and leucopenia. Epirubicin treatment was interrupted or dose reduced if patients developed grade 3 or higher toxicity (dose-limiting toxicity); therefore, the primary analysis compared first-cycle incidence of neutropenia and/or leucopenia $\geq$ grade 3, with body composition measures. First-cycle absolute neutrophil nadir was also used to explore relationships between LBM and chemotherapy toxicity.

Body composition measurements

Anthropometric measurements

Weight and height were recorded according to standard methods. Weight was measured with a medical balance beam scale, and height was measured with a stadiometer. Participants were standing and dressed in light indoor clothing without shoes. Body mass index (BMI) was calculated [weight (kg)/height (m^2)].

Image analysis

Regional muscle tissue was measured by CT from electronically stored images, which had been performed previously for diagnostic purposes. Images taken within 30 days prior to or after initiation of cycle one were selected. There were no interventions (such as surgery) between dates of the CT scan and the start of chemotherapy to alter body composition.

The third lumbar vertebrae (L3) was chosen as a landmark, and two consecutive slices extending from L3 to the iliac crest were assessed to measure cross-sectional area of muscle as described by Shen et al. [20]. Average value from two images was computed for each patient. Images were analyzed using Slice-O-matic software V4.3 (Tomovision, Montreal, QC, Canada). Pre-established thresholds of Hounsfield units (HU) were used, i.e., −29 to 150 for skeletal muscle [18, 19]. Total muscle cross-sectional area was computed for each image. The directly determined unit was area (cm^2) of total L3 skeletal muscle. Total LBM was estimated from muscle cross-sectional areas as described by Mourtzakis et al. [21]: LBM (kg) = 0.30 × [skeletal muscle at L3 using CT (cm^2)] + 6.06; $r = 0.94$; $P < 0.001$, standard error of the estimate: 0.72 kg. Total fat mass was estimated from fat mass cross-sectional areas [21]: whole-body fat mass (kg) = 0.042 × [fat tissue at L3 using CT (cm^2)] + 11.2; $r = 0.88$; $P < 0.001$; standard error of the estimate = 0.80 kg. These are similar to equations reported by Shen et al. [20] for healthy adults, except that regression equations used in the present study were derived from assessing body composition of patients with cancer.

Liver volume is accurately estimated from CT images [22]. Therefore, liver volume (cm^3) was also measured with this technique as described by Lieffers et al. [12]. Because images encompassed the entire liver, the organ tissue surface area on each image was analyzed. Liver surface area on each consecutive image, the image thickness (usually 6.5 mm) and separation (usually 5 mm) were then used by the Slice-O-matic db volumes function to calculate volume. As patients in the study presented with either stage II or III breast cancer, liver metastases were not present and did not need to be considered in liver volume calculations.

Because CT images distinguish body composition components based on their attenuation characteristics, which in turn is a function of tissue density and chemical composition [23], liver mean attenuation (measured in Hounsfield Units, HU) was used to estimate liver fat content: the lower the attenuation, the higher the fat content [23, 24]. Likewise, muscle mean attenuation was also reported.

Determination of epirubicin concentration

An HPLC UV fluorescence detection method adopted from methods of Fogli et al. [25] with modifications was used to measure epirubicin concentrations. The limit of quantification is 10 ng/ml, the range of the standard curve was 10-00 ng/ml, accuracy was better than 95% and precision was less than 13%. Plasma (0.1 ml) was mixed with 0.1-ml dibasic sodium phosphate 0.01 M (pH 6.5) in 5-ml conical centrifuge tubes; they were incubated for 3 h at 37°C and extracted with 1 ml of a chloroform/1-heptanol (9:1 v/v) mixture by gentle shaking on a rotary mixer for 15 min. Samples were centrifuged at 3,000*g* for 10 min; the lower organic phase was transferred to another test tube and re-extracted with 0.175 ml of orthophosphoric acid 0.1 M. Samples were mixed by gentle shaking on a rotary mixer for 10 min and then centrifuged at 3,000*g* for 8 min. The upper aqueous layer was taken off and recentrifuged and filtered (0.2 μm), and 50 μl was then injected onto the chromatographic column.

HPLC separation was performed using a μBondapak Phenyl 10-μm column 300 × 3.9 (Supelco) protected by a μBondpak CN precolumn. Epirubicin was eluted isocratically with a mobile phase consisting of a solution of 50 mM monobasic sodium phosphate–acetonitrile (70:30, v/v) adjusted to a pH 4.0 with orthophosphoric acid. The flow rate was 0.8 ml/min. UV fluorescence detection was done at an λ_{ex} of 480 nm and an λ_{em} of 560 nm.

Pharmacokinetic data were analyzed using NONMEM V (Version 1.1, UCSF, San Francisco, CA, USA), and epirubicin clearance values calculated for each patient. Two approaches were utilized: the first was a literature reported model comprised of a three-compartment structure with various liver function–related covariates. The second used a one-compartment model with the 1- and 24-h plasma concentration samples to evaluate clearance, volume of distribution and specific covariate effects. Both models utilized an exponential inter-individual variability on each of the fixed effects parameters. The three-compartment model utilized a proportional error model, and the one-compartment, an additive and proportional residual error structure (although additive, proportional and combined were tested). Model structural changes and covariate effects were considered significant if the objective function changed >3.84 points for one degree of freedom ($P < 0.05$). The area under the curve (AUC) was calculated from the relationship as follows: AUC = epirubicin dose/(empirical bayes estimate of) clearance.

Statistical analysis

Data entered into the dataset were double entered by two independent people and checked for completeness and accuracy. Exploratory data analyses were performed to better understand the characteristics and patters of the participants/variables, as well as to find trends in the dataset. For quantitative variables, the median and range were calculated. For categorical variables, absolute frequencies were reported. Relationships between variables of interest were also explored by visualization of Loess graphs and scatter plots. A matrix of correlations was calculated between the variables of interest, and it was corrected for multiple comparison problems using Bonferroni correction. The Student's t test for continuous variables was used to examine the bivariate analyses of associations between outcome variables, explanatory variables and potential confounders. The normality assumption was tested through examination of plots (histograms, boxplots, Kernel density plots and Q-Q plots) and the Shapiro–Wilk W test. All P values were two-sided, and levels of significance are $P \leq 0.05$, although clinically important variables were included in the model if their contribution was important and the P value close to $P = 0.05$ [26].

Explanatory variables significant at the bivariate analysis, potential confounders and clinically important variables (age, BSA, BMI, LBM, albumin, urea, liver volume, liver attenuation, bilirubin, tumor stage and AST) were analyzed by applying a systematic multivariable model building. Possible multicollinearity issues among explanatory variables were assessed using the variance inflation factor (VIF) and tolerance (1/VIF—i.e., the degree of collinearity). Variables with VIF > 10 or tolerance < 0.1 are considered to be redundant in the multivariable model and were therefore dropped. Therefore, the final model was consistent with either a simple linear regression or a multiple linear regression depending on the outcome variable of interest. Finally, residual diagnostics were applied to verify linearity assumptions. Statistical analysis was completed using SPSS (SPSS for Windows, version 16.0, SPSS, Chicago, IL, USA) and STATA (StataCorp. 2007, Stata Statistical Software: Release 10. College Station, TX, USA; StataCorp LP).

Results

Patient characteristics

A total of 132 chemotherapy naïve patients were enrolled in the original study, and 24 had CT images that met criteria for analysis of relationships between epirubicin PK/toxicity and body composition. Images selected were on average (±SEM) 19 ± 4.9 days prior to or after initiation of cycle one. Patients who did not have evaluable scans either had no scans on record ($n = 63$), or a scan >30 days from treatment initiation ($n = 28$) or the image would not include the L3 region ($n = 17$). Therefore, 24 women with stage II ($n = 5$) or III ($n = 19$) breast cancer were included in the present analysis. Liver assessment for one patient was not possible due poor image quality. Patient characteristics are described in Table 1, and frequencies of epirubicin-associated toxicities are shown in Table 2. Patients presented with a wide range of body composition with LBM ranging over 2 times (32.9–67.3 kg) and fat and liver masses ranging over 4 times (13–53.6 kg and 0.9–4.6 kg, respectively). Estimated epirubicin dose per kg of LBM ranged from 3.3 to 5.1 mg/kg. A wider variation (~4 times) was observed if dose was adjusted by cm^3 of liver volume, Table 1. No correlations were observed between liver volume and age, but liver volume was strongly correlated with LBM ($r = 0.87$, $P < 0.001$).

The relationship between LBM vs. BSA and liver volume and BSA is shown in Fig. 1a and b, respectively. Patients with same BSA presented with a wide variation in LBM and liver volume. Liver attenuation in HU varied over 5 times (Table 1) and was negatively associated with liver mass ($r = -0.7$, $P < 0.0001$), implying that an

Table 1 Patient characteristics ($N = 24$)

Variables	Median (range)
Age (years)	52.5 (28.1–67.1)
Body mass index (kg/m^2)	27.6 (19.4–44.4)
Body surface area (m^2)	1.8 (1.3–2.3)
Muscle cross-sectional area (cm^2)	122.5 (89.4–204.0)
Muscle attenuation (HU)	36.0 (22.0–55.5)
Estimated total lean body mass (kg)[a]	42.8 (32.9–67.3)
Fat cross-sectional area (cm^2)	351.8 (41.2–1,009.8)
Estimated total body fat mass (kg)[b]	26.0 (13.0–53.6)
Liver volume (cm^3)[c]	1,520 (888–4,378)
Liver attenuation (HU)[c]	111.7 (34.2–165.9)
Aspartate transaminase (U/l)	22.0 (14.0–43.0)
Total bilirubin (μmol/l)	7.0 (4.0–16.0)
Epirubicin clearance (l/h)	61.7 (33.3–107.9)
Epirubicin/LBM estimate (mg/kg)	4.3 (3.3–5.1)
Epirubicin/liver volume (mg/cm^3)[c]	0.12 (0.05–0.17)

[a] Calculated from regression equations from Mourtzakis et al. [21]: Whole-body lean mass (kg) = 0.30 × [skeletal muscle at L3 using CT (cm^2)] + 6.06

[b] Whole-body FM (kg) = 0.042 × [fat tissue at L3 using CT (cm^2)] + 11.2

[c] $N = 23$ (1 missing variable)

Table 2 Frequencies of toxicities experienced by patients

Toxicity	Grade[a]			
	1	2	3	4
Nausea	6		3	
Vomiting	1	1	2	
Mucositis	7	1		
Neutropenia		2	3	19
Febrile neutropenia			2	
Leucopenia	2	7	12	1
Insomnia	2	1		
Alopecia	4	2		
Constipation	3	3		

[a] NCI common toxicity criteria version 2.0

increase in liver size was associated with a decrease in HU (the larger the liver, the higher the fat content). In addition, liver attenuation was positively correlated with muscle attenuation ($r = 0.5$, $P = 0.025$).

LBM and epirubicin toxicity

Only 2 (8.3%) patients did not present with toxicity. The mean LBM of the toxicity-absent group was higher compared to toxicity-present group (56.2 vs. 41.6 kg, $P = 0.002$, Fig. 2a). LBM was also positively correlated with neutrophil nadir ($r = 0.5$, $P = 0.023$, Fig. 2b).

LBM and epirubicin PK

PK model

The three-compartment model resulted in an objective function value that was 1,000 points higher than the simpler one-compartment model. Hence, we adopted the one-compartment model strategy for this analysis. None of the covariates were significant in the one-compartment model approach. Models were run using the first-order conditional estimation method with interaction. Empirical Bayes estimates for clearance were extracted and used for comparisons with covariates as well as for calculating individual level AUC.

Clearance

A wide variation in drug clearance was observed: 33.3–107.9 l/h (Table 1). In order to meet normality assumptions, logarithm transformation was applied to clearance (log-clearance). Linear regression analysis demonstrated a significant association between log-clearance and LBM ($P = 0.041$, Fig. 3) and moderate association between log-clearance and AST ($P = 0.055$), with Pearson's correlation of 0.43 and 0.41, respectively, Table 3. Therefore, LBM alone predicted 18% variability in epirubicin clearance. Log-clearance was not associated with age, BSA, fat mass, albumin, urea, liver volume, liver attenuation, bilirubin or tumor stage.

Verification of confounders, influential points and outliers were performed during and after the multivariable model building. Partial F tests were conducted to select the final model that better predict log-clearance with the minimum number of explanatory variables (parsimonious model). The final main effects model for log-clearance included LBM and AST. For one kilogram unit increase in LBM, there was approximately 19% increase in the rate of clearance, after adjusting for the effect of AST. Likewise, for one unit increase in AST, there was approximately 2% decrease in the rate of clearance, after adjusting for LBM effects. This regression model significantly predicted log-clearance and explained approximately 33% of its variance (Table 3).

Epirubicin AUC

Epirubicin AUC was investigated as a secondary variable of epirubicin PK. After controlling for confounding variables (age, BSA, LBM, fat mass, albumin, urea, liver volume, bilirubin and tumor stage), the best model to predict AUC

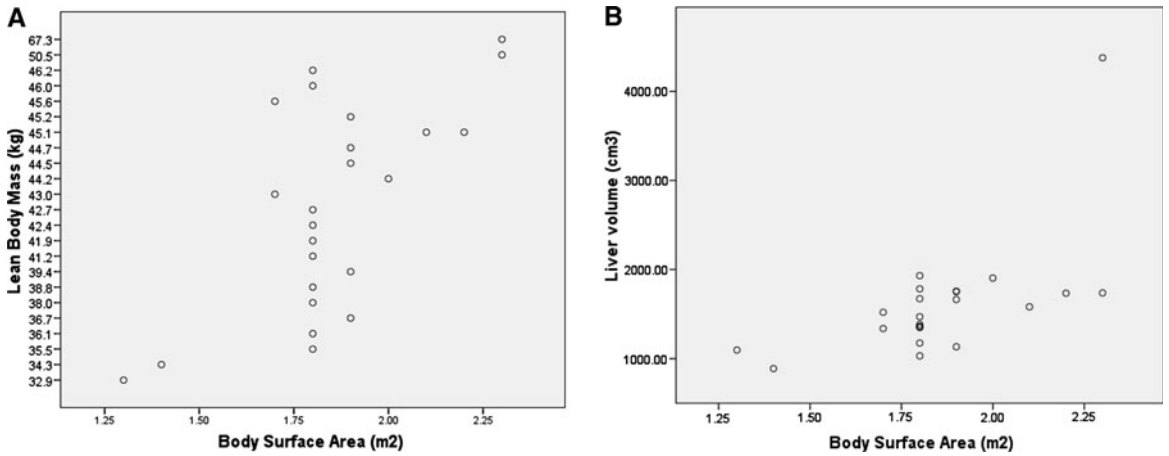

Fig. 1 **a** Relationship between lean body mass (LBM) and body surface area (BSA) and **b** relationship between liver volume and BSA

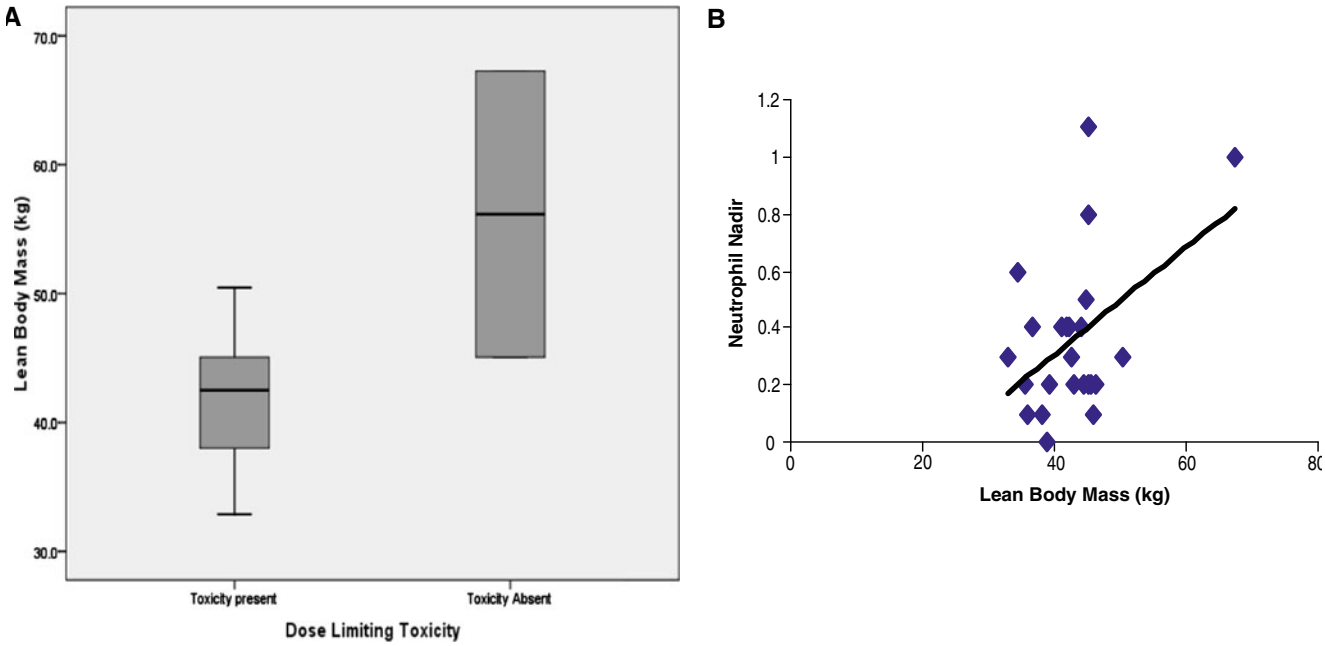

Fig. 2 **a** Relationship between lean body mass (LBM) and dose-limiting toxicity ($P = 0.002$ *t* test). **b** Relationship between LBM and neutrophil nadir ($r = 0.5$, $P = 0.023$)

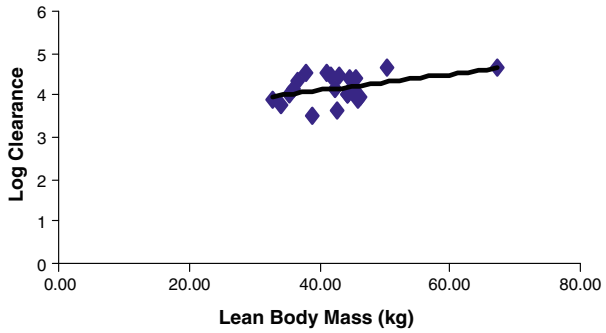

Fig. 3 Relationship between plasma epirubicin clearance and lean body mass ($r = 0.43$, $P = 0.041$)

included AST and liver attenuation (as a dichotomous variable in relation to median <112 HU, $n = 12$ and ≥112 HU, $n = 11$; 1 missing variable), Table 3.

Discussion

In a classic paper reviewing LBM use on drug dosage, Morgan and Bray [8] highlighted the lack of studies investigating LBM as a predictor of drug clearance [8]. To our knowledge, this is the first study to investigate the ability of LBM, liver size, liver attenuation and function to

Table 3 Model building for clearance and AUC

Explanatory variables	Clearance			Explanatory variables	AUC		
	Coefficient	95% CI[a]	*P* value		Coefficient	95% CI[a]	*P* value
Bivariate analysis							
Intercept	–	–	–	Intercept	–	–	–
LBM	1.02	1.00–1.04	0.041	Liver attenuation[b]	1.55	0.31–2.79	0.017
AST	0.98	0.96–1.00	0.055	AST	0.13	0.02–.24	0.024
Multivariate analysis							
Intercept	46.06	18.11–117.43	<.0001	Intercept	3.72	0.27–7.18	0.036
LBM	1.02	1.00–1.04	0.045	Liver attenuation[b]	1.65	0.51–2.79	0.007
AST	0.98	0.96–1.00	0.063	AST	0.13	0.04–0.23	0.010

LBM lean body mass, *AUC* area under the curve, *AST* aspartate aminotransferase

[a] Values were rounded up

[b] High liver attenuation (greater than median) as reference group, $N = 23$ (1 missing variable)

[c] Regression adjusted for effect of age; $N = 23$ (1 missing variable)

predict epirubicin PK. Using CT imaging, a state-of-the-art methodology to assess body composition, we confirmed the great variability of LBM, fat mass and liver volume in our cohort of women with breast cancer [11, 16]. We demonstrated a wide variation in LBM and liver size in patients with same body size (i.e., same BSA) and confirmed that lower LBM is associated with a greater incidence of toxicity and lower absolute neutrophil count for patients receiving epirubicin treatment. Importantly, LBM and AST explained 33% of the variation in epirubicin clearance providing proof of principle of LBM relationship with epirubicin PK. Lean body mass varied greatly among patients with the same BSA, producing great variability in drug dose per unit LBM [10].

There is mounting evidence to suggest that LBM is better than BSA in predicting drug efficacy and toxicity. Our study supports this and adds an additional class of antineoplastic agent (anthracyclines) to which this applies. Although toxicity results presented here also reflect effects of other drugs in the FEC regimen (i.e., 5FU and cyclophosphamide), similar findings with patients receiving 5FU treatment [10] and the observed relationship between LBM and epirubicin clearance allow us to trust this finding. Furthermore, multivariate linear regression confirmed the independent contribution of LBM to epirubicin pharmacokinetics, as 33% of the variability in epirubicin clearance was explained by LBM and AST. The effect of LBM in predicting epirubicin clearance has been previously suggested in a preliminary study ($n = 10$) by Cosolo et al. [27]. They reported a good correlation between LBM and epirubicin clearance ($r = 0.65$, $P < 0.05$) and suggested further studies to evaluate the observed relationship. Unfortunately, limitations to the study included small sample size and the use of a single explanatory variable (simple linear regression). Furthermore, associations between LBM and chemotherapy toxicity were not reported. Here, we explored several variables of clinical importance in predicting epirubicin clearance with a somewhat larger sample size and a statistical approach including LBM and AST, which is the most reliable measure currently known in predicting epirubicin clearance [28]. Therefore, although LBM was an independent and significant predictor of epirubicin PK, a model combining LBM and AST better predicted variability in clearance.

One of the main organs responsible for epirubicin metabolism is the liver [13], which contributes to LBM. While it has been proposed that correlations between hepatic clearance and LBM may be due to LBM being a surrogate marker for liver volume [8], our analysis suggests LBM, but not liver mass per se, predicted epirubicin clearance. The explicit relationship between LBM and liver volume and epirubicin clearance would be difficult to discriminate because LBM and liver volume are strongly correlated. Liver volume was inversely associated with liver attenuation, suggesting that larger livers were more likely to be infiltrated with fat. In that case, there may not be a strong association between liver volume and functional hepatic parenchymal mass (number of hepatocytes and hepatic blood flow). Altered AST concentration may be another indicator of altered hepatic function. It is known that higher AST concentrations (and other liver enzymes) are associated with decreased clearance of epirubicin [28] and other drugs [29]. Liver attenuation (degree of fat infiltration) and AST were associated with AUC, and since both of these are markers of steatosis, this condition may be a factor influencing epirubicin exposure. Liver attenuation was also associated with muscle attenuation implying that fat infiltration in both tissues may be a related whole-body process.

Limitations of the present exploratory study include the relatively small sample size, which nonetheless provides some interesting observations, suggesting that different elements of the body composition may influence drug PK. Although epirucibin is a hydrophobic drug, we observed no relationship between estimated whole-body fat mass and epirucibin PK. However, interesting relationships were observed when liver volume and LBM were studied. The LBM is the sum of organs and tissues of different types, which exist in different proportions in individual patients and which can each make a distinct contribution to drug metabolism. In relation to liver, multiple correlates of hepatic clearance may play a role. These include not only liver volume, but hepatic enzyme activity and other physiological parameters associated with the LBM compartment [29]. Understanding how different body composition compartments are related to epirubicin metabolism cannot be simplified. Arcamone et al. [7] reported epirubicin's tissue-specific metabolism using radioactive compounds. According to the authors, significant amounts of the drug were found in the liver and kidneys; in relation to muscle mass (LBM component), the activity of drug per grams of muscle was approximately 1/5 of that observed in liver. However, muscle is a much larger tissue compared to liver (2 kg of liver vs. 20 kg of muscle in a healthy adult), which could lead to a larger contribution to the drug's volume of distribution. Moreover, epirubicin is highly protein bond (77%), and we hypothesize that binding also occurs at the LBM level rather than exclusive to serum albumin.

We conclude that LBM predicts epirubicin clearance and may be a better measure with which to individualize treatment than the current convention of normalizing the dose to BSA. This concept warrants validation in prospective trials testing LBM-based epirubicin dosing.

Acknowledgments We thank Laura Birdsell for her assistance with body composition analysis, Linda Harris for her bibliographic expertise, Edith Pituskin, Sambasivarao Damaraju, Andrew G. Scarfe, Mark Clemons, Katia Tonkin, Heather-Jane Au, Sheryl Koski, Anil A. Joy, Michael Smylie, Karen King and Diana Carandang for their assistance with data collection. Roche Fellowship in Translational Research from Alberta Cancer Foundation (CMMP), Alberta Heritage Foundation for Medical Research (AHFMR) Fellowship (CMMP), Canadian Breast Cancer Research Alliance (MBS), Alberta Cancer Foundation (ACF) and Canadian Institute of Health Research (MBS). The authors had full control of all primary data and agree to allow the journal to review the data if requested. M. B. Sawyer—Research and Travel (ASCO) Funding from Pfizer Oncology, J. R. Mackey—Honoraria from Pfizer Oncology.

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