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Rien H. L. Hoge, PharmD, PhD,†‡ Suzan E. H. Detert Oude Weme, PharmD, MSc,†§ Walter L. Vervenne, MD, MSc,¶ Inge R. F. van Berlo-van de Laar, PharmD, PhD,† Carla M. L. van Herpen, MD, PhD,‖ Laurens Roorda, PharmD, MSc,* Ron A. A. Mathôt, PharmD, PhD,** Maartje S. Jacobs, PharmD, MSc,†§ Nielka P. van Erp, PharmD, PhD,‡ and Frank G. A. Jansman, PharmD, PhD†§*

Abstract:

Aim: This study examined whether anthropometric and body composition parameters such as body surface area (BSA), lean body mass (LBM), and total body weight (TBW) are correlated with docetaxel clearance and exposure by analyzing area under the curve. In addition, LBM, TBW, and a fixed dose were compared with BSA as dosing parameters for dose individualization of docetaxel.

Methods: Thirty-six patients receiving docetaxel chemotherapy for breast or metastatic castration-resistant prostate carcinoma were included. Before treatment, LBM was measured using a dual-energy X-ray absorptiometry scanner. Blood samples were collected up to 180 minutes after dosing to analyze docetaxel concentrations and determine individual pharmacokinetic parameters.

Results: No significant correlations were found between docetaxel clearance and the anthropometric and body composition variables (BSA, LBM, and TBW). The area under the curve was significantly but poorly correlated with BSA [r = 0.452 (P = 0.016)] and TBW [r = 0.476 (P = 0.011)]. The mean absolute percentage error and mean error of simulated dosing based on LBM and fixed dosing were not significantly different from those of BSA. For TBW, only mean absolute percentage error was significantly higher compared with dosing based on BSA (24.1 versus 17.1, P = 0.001).

Conclusions: There was no clinically relevant correlation between docetaxel pharmacokinetics and the anthropometric and body composition variables BSA, LBM, and TBW. Therefore, dose individualization of docetaxel based on LBM, TBW, or fixed dosing cannot be recommended over BSA-based dosing.

Key Words: docetaxel, pharmacokinetics, body composition, drug dosing, body surface area

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INTRODUCTION

Docetaxel is a semisynthetic taxane-derived neoplastic agent used to treat breast and metastatic castration-resistant prostate carcinoma (mCRPC) along with several other cancers.[8] Pharmacokinetics of docetaxel show high interindividual clearance variability, which may result in underdosing or overdosing.[1] To reduce this variability, dosing is currently based on body surface area (BSA).[2]

BSA-based dosing results have high interindividual drug exposure variability for most anticancer drugs, leading to undesirable side effects or insufficient tumor responses. Because of this, it is highly debated whether BSA-based dosing should be the method of choice for dosing chemotherapeutics.[1,3] Pharmacokinetic parameters such as clearance and area under the curve (AUC) are known markers for predicting therapeutic responses.[2] A study by Engels et al[4] showed that therapeutic drug monitoring (TDM) significantly decreased the interindividual variability in docetaxel exposure when compared with BSA-based dosing. Although TDM is an elegant method for dose optimization, it is very labor-intensive and costly in the clinical setting; alternative anthropometric parameters that correlate better with drug exposure should be considered to optimize anticancer drug dosing.[5,6]

Docetaxel doses ranging from 75–100 mg/m^2 were given once every 3 weeks during a 1-hour intravenous infusion. Docetaxel is metabolized in the liver through oxidation by cytochrome P450 (CYP)3A4 and CYP3A5 and is 95% bound to albumin without significant renal clearance.[7–9] The

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From the *Department of Clinical Pharmacy, Wilhelmina Hospital Assen, Assen, the Netherlands; †Department of Clinical Pharmacy, Deventer Hospital, Deventer, the Netherlands; ‡Department of Pharmacy, Radboud Institute of Health Sciences, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; §Unit of Pharmacotherapy, Epidemiology, and Economics, Groningen Research Institute of Pharmacy (GRIP), University of Groningen, Groningen, the Netherlands; ¶Department of Internal Medicine, Deventer Hospital, Deventer, the Netherlands; ‖Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands; and **Department of Pharmacy, Academic Medical Centre, Amsterdam, the Netherlands.

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R. H. L. Hoge and S. E. H. Detert Oude Weme shares (co-)first authorship.

The study was conducted in accordance with the Declaration of Helsinki.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Correspondence: Suzan E. H. Detert Oude Weme, PharmD, MSc, Department of Clinical Pharmacy, Deventer Teaching Hospital, Nico Bolkesteinlaan 75, 7416 SE Deventer, the Netherlands (e-mail: s.detertoudeweme@dz.nl).

pharmacokinetics of docetaxel can be best described by a 3-compartment model with α, β, and γ half-lives of 4.5 minutes, 38.3 minutes, and 12.2 hours, respectively. AUC increases proportionally with increasing doses, and docetaxel is distributed in tissues with a mean volume of distribution (VD) of 74 L/m^2.[7] Docetaxel is characterized by highly interindividual pharmacokinetic variation, with up to 10-fold differences in drug clearance in patients with normal hepatic function.[10] Bruno et al[11] found that the median docetaxel clearance was 36.6 L/h (5th to 95th ranging from 17.5 L/h to 59.3 L/h). This variability may lead to adverse effects, suboptimal treatment, or even treatment failure. The primary major adverse effect is neutropenia, which is dose-limiting in most cases.[7] Other frequently occurring side effects of docetaxel are anemia, alopecia, nausea, asthenia, peripheral neuropathy, fluid retention, and nail toxicity.[8,9]

Lean body mass (LBM) could be an alternative dosing parameter to BSA because LBM has been shown to correlate better than BSA or total body weight (TBW) with drug clearance of cisplatin, paclitaxel, and troxacitabine in obese patients.[14] In addition, LBM has been investigated as a dosing parameter for several anticancer drugs.[5,13–21]

Patients with comparable BSA values are known to have a wide variety of liver volumes and LBM.[22,23] Because liver volume is strongly correlated with LBM, and docetaxel is mainly metabolized by the liver, it is hypothesized that individual dosing based on LBM should be better than that based on BSA.[22,23]

This study aimed to determine which anthropometric and body composition parameters (BSA, LBM, and TBW) correlated best with docetaxel clearance (CL) and exposure (expressed in AUC). In addition, LBM, TBW, and a fixed dose were compared with BSA as dosing parameters for dose individualization of docetaxel.

MATERIALS AND METHODS

Patients and Study

A multicenter prospective study of patients treated with docetaxel was performed. Patients who received docetaxel chemotherapy for breast cancer or mCRPC were included. Docetaxel in breast cancer treatment was a part of a combined treatment with cyclophosphamide and doxorubicin as adjuvant or neoadjuvant therapy. In patients with CRPC, docetaxel was administered as monotherapy. Other criteria for inclusion were an absolute neutrophil count $>1.5 \times 10^9$/L, serum creatinine ≤2x upper limit of normal (ULN), and total bilirubin <1.5 ULN. The exclusion criteria were docetaxel use in the previous year, moderate or severe liver impairment [alkaline phosphatase and transaminases (ALAT and/or ASAT) ≥ 1.5 ULN and alkaline phosphatase (ALP) ≥ 2.5 ULN], and current therapy with any drug, dietary supplements, or other compounds known to inhibit or induce CYP3A4. Every patient received either 75 or 100 mg/m^2 of docetaxel dissolved in saline solution infused over 1 hour.

The estimation of the study population size (36 participants) was derived from studies by Gusella and Prado.[5,13] The study was conducted in accordance with the Declaration of Helsinki, and all study participants provided written informed consent before study entry.

Body Composition Measurements

TBW was measured using a medical body weight scale (kg). A fixed stadiometer was used to determine patient height while standing barefoot against a straight wall. LBM was measured using a dual-energy X-ray absorptiometry scanner. In the Deventer Teaching Hospital, patients were scanned using a GE Lunar scanner (GE Healthcare, Little Chalfont, United Kingdom), whereas patients in Radboud University Medical Center were scanned using a Hologic Discovery scanner (Hologic, Bedford, MA).

PK Sampling and Analysis

Pharmacokinetic blood samples were obtained at t = 0 (before infusion) and t = 30 minutes, t = 55 minutes (before the end of infusion), and t = 180 minutes after the start of infusion according to a validated limited sampling strategy.[11,24,25] NONMEM software (ICON, Dublin, Ireland) was used to perform a Bayesian analysis using the population PK model reported by Bruno et al.[26] The model incorporated BSA, α_1-acid glycoprotein (AAG), albumin, and hepatic function [elevated levels of ALAT and ASAT], and age as the main predictors of docetaxel CL. Based on the population PK model and the observed individual plasma concentrations, individual PK parameter estimates (CL and VD) were obtained by Bayesian (post hoc) analysis.

Bayesian estimation for individual CL was used to calculate the individualized AUC based on the individualized dose according to the following formula:

$$\mathrm{AUC} = \frac{\mathrm{Dose\ (D)}}{\mathrm{Clearance\ (CL)}}$$

Chemicals and Reagents

Docetaxel and paclitaxel (internal standards) used for the preparation of calibrators or quality control samples were supplied by Sanofi-Aventis (Frankfurt am Main, Germany) and Sigma-Aldrich (Schnelldorf, Germany), respectively. Acetonitrile and methanol were purchased from POCH (Gliwice, Poland). KH_2PO_4 (ACS quality) was purchased from J. T. Baker (Deventer, Netherlands). Tert-butylmethyl ether was supplied by LiChrosolv (Merck, Darmstadt, Germany). Milli-Q water was purified using Q-Pod (Merck Millipore, Milford, MA).

Docetaxel Analysis

Docetaxel plasma concentrations were quantified using high-performance liquid chromatography ultraviolet (HPLC-UV). In brief, 20 μL of internal standard solution (50 mcg/mL paclitaxel in methanol) was added to 1000 μL of plasma aliquots. Liquid–liquid extraction was performed using 5 mL of tert-butyl methyl ether as the extraction fluid. The solution was shaken for 5 minutes and centrifuged at approximately 3500*g* for 5 minutes. Subsequently, the plasma layer was frozen in a cryobath, and the organic layer was isolated and evaporated using compressed air. The residue was

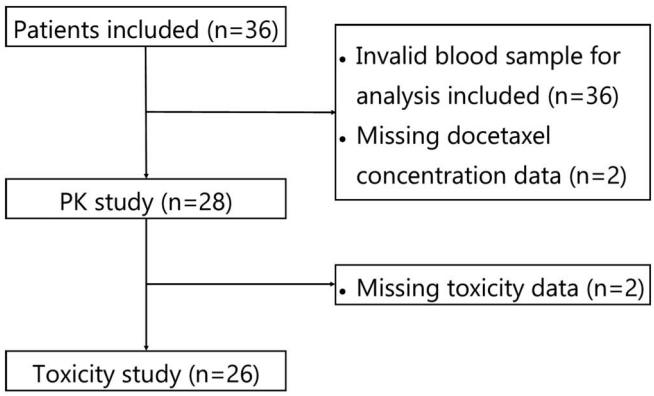

FIGURE 1. Flowchart of included patients.

reconstituted with 150 μL of methanol/Milli-Q (1:1), and 75 μL was injected into the Shimadzu Prominence HPLC system (Shimadzu USA, Canby, OR). Chromatographic separation was achieved using a Varian Chromsep SS Omnispher 5 C18 column (100 × 3 mm I.D., particle size 3 μm, Agilent Technologies, Amstelveen, Netherlands). The mobile phase was composed of 0.02 mol/L acetonitrile/phosphate buffer (40:60 vol/vol) and delivered with an isocratic flow of 1.0 mL/min. The overall run time was 12 minutes. The UV detection wavelength was set to 230 nm. The quantification was based on a freshly prepared calibration curve of 6 calibration standards and a blank sample (0, 50, 150, 500, 1000, 2000, and 4000 ng/mL). In each run, 2 QC samples (750 and 3000 ng/mL) were analyzed in duplicate. The method was validated in line with the European Medicines Agency Guideline on bioanalytical validation.[27] The calibration curve was found to be linear in the 50–4000 ng/mL range, with a correlation coefficient (R^2) of 0.9987. The within-run and between-run accuracy (at 200, 750, and 3000 ng/mL) ranged from 91% to 106%. The within-run and between-run precision correlation coefficients ranged from 1.3% to 14.1%.

Biochemical Parameters

As part of the standard hospital protocol, hematology and biochemistry assessments were performed before each chemotherapy course: ASAT, ALAT, gamma-glutamyltransferase, ALP, AAG, albumin (ALB), total bilirubin, creatinine, hemoglobin (Hb), hematocrit (Ht), red cell count (RBC), platelet count, total white cell count (WBC), and differential white cell count were all evaluated.

Data and Statistical Analysis

Data are expressed as median with interquartile range (IQR). The median values obtained for women and men were compared using the Mann–Whitney *U* test for unpaired data. The accepted significance level was set at $P < 0.05$. Linear regression analysis was used to compare the correlations between BSA, LBM, and TBW with docetaxel clearance and exposure. Correlations were evaluated by

TABLE 1. Patient Characteristics and Pharmacokinetic Parameters

Variables	Males	Females	Total	*P*
No. of patients	5	23	28	—
Patient characteristics				
Age (yrs)	69.60 (16.3)	56.00 (12.9)	56.25 (12.0)	0.024*
Body surface area (m^2)	2.10 (0.31)	1.85 (0.28)	1.89 (0.31)	0.059
Total body weight (kg)	89.50 (28.30)	73.10 (19.30)	74.55 (19.80)	0.067
Lean body mass (kg)	54.54 (7.74)†	45.65 (8.35)	45.84 (9.62)†	0.017*
AAG ($g \cdot L^{-1}$)	1.06 (0.31)	0.91 (0.33)	0.95 (0.37)	0.490
Albumin ($g \cdot L^{1}$)	37.60 (5.90)	37.50 (5.10)	37.55 (4.55)	0.674
Total bilirubin ($\mu mol \cdot L^{1}$)	10.00 (19.00)	5.5 (1.00)	6.00 (2.00)	0.080
ASAT ($U \cdot L^{-1}$)	29.00 (34.00)	24.00 (34.00)	26.50 (9.75)	0.171
ALAT ($U \cdot L^{-1}$)	18.00 (13.00)	27.00 (18.00)	25.00 (18.50)	0.110
ALP ($U \cdot L^{-1}$)	90.00 (41.50)	75.00 (24.50)	80.00 (26.00)	0.329
GGT ($U \cdot L^{-1}$)	46.00 (92.75)	27.00 (25.50)	28.50 (28.50)	0.088
PK parameters				
Docetaxel dose (mg)	160 (18)	140 (20)	140 (25)	0.040*
Docetaxel/BSA ($mg \cdot m^{-2}$)	76.19 (2.8)	75.58 (1.8)	75.59 (1.7)	0.741
Docetaxel/LBM ($mg \cdot kg^{-1}$)	2.80 (0.2)	3.09 (0.3)	3.07 (0.4)	0.020*
Docetaxel/TBW ($mg \cdot kg^{-1}$)	1.77 (0.3)	1.88 (0.2)	1.88 (0.2)	0.168
Clearance ($L \cdot h^{-1}$)	44.41 (6.57)	47.64 (14.17)	47.04 (10.94)	0.453
AUC ($mg \cdot h \cdot L^{-1}$)‡	3.43 (0.61)	3.05 (0.78)	3.13 (0.70)	0.067
Distribution volume (L)	8.71 (4.13)	8.88 (2.76)	8.79 (2.65)	0.569

Data are presented as the median (IQR).
*Significant differences between men and women at the 0.05 level (Mann–Whitney *U* test).
†Total number of LBM data = 27. One male patient missed the LBM data.
‡Calculated from the equation: AUC = Dose/CL
GGT, gamma-glutamyltransferase.

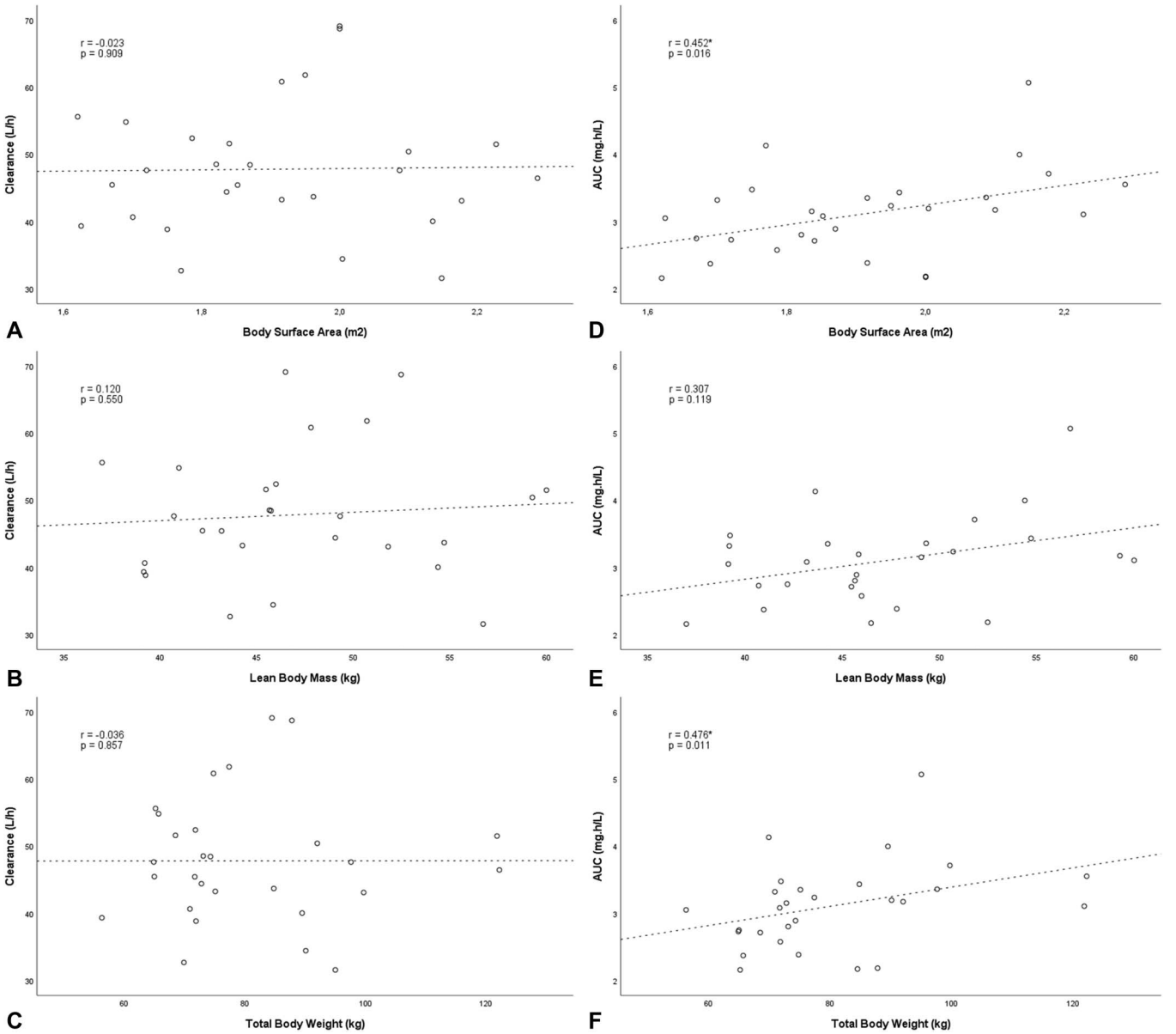

FIGURE 2. Possible correlation between anthropometric and body composition variables and docetaxel pharmacokinetic parameters, r = Spearman correlation coefficient. A = BSA and CL, B = LBM and CL, C = TBW and CL, D = BSA and AUC, E = LBM and AUC, and F = TBW and AUC. *Correlation is significant at the 0.05 level (2-tailed). ‡Total number of LBM data = 27. One male patient missed LBM data.

determining Spearman correlation coefficients with the corresponding P values.

Different doses were simulated based on individual anthropometric and body composition parameters as well as the median docetaxel/BSA, docetaxel/LBM, docetaxel/TBW, and docetaxel dose (referred to as the fixed dose). The optimal target AUC was assumed to be the recommended docetaxel dose of 75 mg/m^2 divided by all individual clearance values corrected for BSA.

The difference between the optimal target AUC and simulated AUC results was evaluated by calculating accuracy using the following formula for MAPE:

$$\mathrm{MAPE} = \frac{1}{n}\sum \left|\frac{\mathrm{AUCsim} - \mathrm{AUCtarget}}{\mathrm{AUCtarget}}\right| \times 100,$$

where AUCsim denotes the simulated AUC results and AUCtarget denotes the optimal target AUC.

Bias was calculated using the following ME formula:

$$\mathrm{ME} = \frac{1}{n}\sum (\mathrm{AUCsim} - \mathrm{AUCtarget}),$$

where AUCsim denotes the simulated AUC results and AUCtarget denotes the optimal target AUC.

TABLE 2. Mean Absolute Percentage Error (Accurary) and Mean Error (Bias) for Different Simulated Dosing Methods

	AUC_{BSA}	AUC_{LBM}	AUC_{TBW}	$AUC_{fixeddose}$
Mean ± SD	3.14 ± 0.71	3.13 ± 0.77	3.29 ± 0.94	3.04 ± 0.60
MAPE (95% CI)* (%)	17.1 (11.3 to 22.8)	18.4 (12.2 to 24.7)	24.1 (17.1 to 31.2)	15.0 (10.2 to 19.7)
P†	Reference	0.361	0.001‡	0.362
ME (95% CI)* ($mg \cdot h \cdot L^{-1}$)	0.01 (−0.27 to 0.28)	0.00 (−0.30 to 0.31)	0.16 (−0.21 to 0.52)	−0.09 (−0.32 to 0.14)
P†	Reference	0.943	0.145	0.255

*Assuming an optimal target AUC of 3.13.
†*P* calculated with the Wilcoxon signed-rank test; the reference value is MAPE and ME of AUC_{BSA}.
‡Difference from the reference is significant at the 0.05 level (2-tailed).

Toxicity

Toxicity due to chemotherapy was scored by physicians during all treatment cycles according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[28] Only grade 3 and 4 toxicities were considered in the analysis. Premature therapy termination (patients who did not complete the standard 6 or 10 cycles), dose delay (patients needing >3 weeks to recover from chemotherapy), and dose reduction because of toxicity were recorded. Overall toxicity was defined as toxicity ≥ grade 3, dose delay, dose reduction, or premature treatment termination due to toxicity.

RESULTS

A total of 36 patients, of whom 28 were female, were included in the study at the Deventer Teaching Hospital (n = 20) and Radboud University Medical Center (n = 16). Docetaxel data from 8 subjects were not evaluated because blood was collected from 6 patients in the infusion arm and 2 patients refrained from blood sampling. Two patients were lost to follow-up for the toxicity data. Figure 1 shows the flowchart of the included patients.

Patient characteristics, main demographics, anthropometric measures, body composition, and docetaxel pharmacokinetic parameters for the men, women, and the entire study population are shown in Table 1. Women had a significantly lower median age than men [56 (12.9) versus 69.6 (16.3), $P = 0.024$]. This is likely because docetaxel is administered primarily to women with breast cancer, which is mostly diagnosed at a younger age than CRPC in men. Another significant difference was the lower LBM in women than in men [45.7 (8.4) versus 54.5 (7.7), $P = 0.017$], which was in accordance with literature data.[14,29] None of the pharmacokinetic parameters differed between men and women, except for dose [women 140 (20) versus men 160 (18), $P = 0.040$] and dose/LBM [women 3.09 (0.3) versus men 2.80 (0.2), $P = 0.020$].

Correlation of Anthropometric and Body Composition Parameters

No significant correlations were found over the entire population between the docetaxel pharmacokinetic CL and the anthropometric and body composition variables (BSA, LBM, and TBW). The AUC was significantly but poorly correlated with BSA and TBW (Fig. 2). In addition, no significant correlations were found between VD and BSA, LBM, or TBW.

Simulation of Dosing Methods

The results of the simulated dosing methods based on median BSA, LBM, TBW, and fixed dosing are presented in Table 2 and illustrated in Figure 3. The optimal target AUC was calculated as 3.13 $mg \cdot h^{-1} \cdot L^{-1}$. For evaluation of the simulated doses, MAPE for accuracy and ME for bias were calculated and are shown in Table 2. The MAPEs and MEs of simulated dosing based on LBM, TBW, or fixed-dosing ME were not significantly different from those for dosing based on BSA. The MAPE of dosing based on TBW was significantly higher than that of BSA ($P = 0.001$).

Toxicity Correlations

Nine of 26 patients (34.6%) experienced severe toxicity (≥grade 3). One patient experienced grade 3 mucositis, 5 patients experienced grade 3 or 4 neutropenia, and 7 patients had other forms of toxicity (fatigue, febrile neutropenia, hyperglycemia, infection, leukopenia, and polyneuropathy). No significant relationships were found between any of the pharmacokinetic parameters, any of the anthropometric/body composition parameters, docetaxel dose, docetaxel/BSA, docetaxel/LBM, or docetaxel/TBW, and overall toxicity.

DISCUSSION

To the best of our knowledge, this is the first study to examine the relationship between the pharmacokinetics of docetaxel and the anthropometric and body composition parameters BSA, LBM, and TBW. No correlations were found between the CL or VD of docetaxel and the anthropometric and body composition parameters. Exposure (expressed in AUC) was significantly but poorly correlated with BSA and TBW, with Spearman correlation coefficients of 0.452 ($P = 0.016$) and 0.476 ($P = 0.011$), respectively. In addition, docetaxel dosing based on LBM and TBW or fixed dosing was not found to be superior to BSA after simulated dosing.

Over the past 2 decades, there has been an increase in the number and homogeneity of studies investigating the influence of body composition on chemotherapy published, which suggests a correlation between body composition parameters other than BSA with chemotherapy pharmacokinetics and toxicity.[5,13–21] One example is a study with 1206 adult patients with cancer, of whom 162 were obese (body mass index ≥ 30), in which the absolute clearance of cisplatin, paclitaxel, and troxacitabine was significantly higher

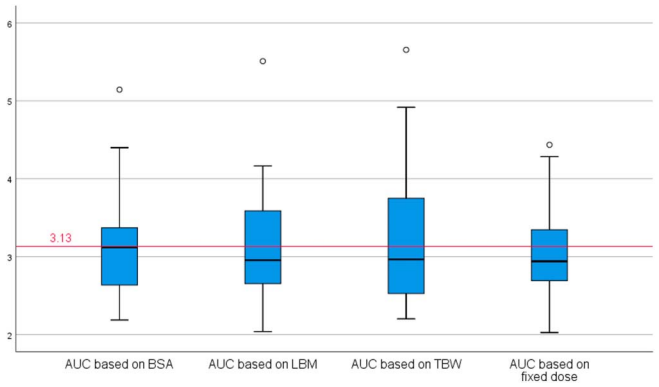

FIGURE 3. Boxplots of AUC based on BSA, LBM, TBW, or fixed dose with the reference line AUC_{target} = 3.13.

in obese patients.[14] For docetaxel and doxorubicin, the authors concluded that applying LBM as a dosing scalar was of particular merit.[14] The present study included 9 obese patients (32.1%), but no significant correlation was found between any of the anthropometric or body composition parameters and docetaxel pharmacokinetics. Another study correlated LBM with epirubicin log-clearance with a Pearson correlation of 0.43.[15] The present study found significant Spearman correlations of 0.45 and 0.48 for BSA and TBW with docetaxel AUC, respectively. In contrast to the epirubicin study, this variable was not applied in a systematic multivariable model.

Several other studies have highlighted differences in drug dosing by LBM. These studies indicated that patients with dose-limiting toxicities (DLTs) had higher doses of gemcitabine, vinorelbine, carboplatin, pemetrexed, oxaliplatin, and sunitinib per kg LBM.[18–21] Unlike Xing et al,[30] the present study found no trend of a higher docetaxel to LBM ratio in patients who experienced overall toxicity compared with patients who did not. Nine patients experienced severe toxicity, which resulted in 7 experiencing dose delay, reduction, or termination of treatment. Five patients (19.2%) experienced grade 3 or 4 neutropenia, which was a lower proportion than that reported in other studies.[11,30]

In contrast to most other studies, no correlations were found between the CL of docetaxel and BSA, LBM, or TBW. Consequently, the results of this study do not support the application of any of these parameters for the individualization of docetaxel therapy. This includes BSA, which is widely used in daily practice. A fixed-dosing method was used in the dosing simulation performed in this study; strikingly, a fixed dose of 140 mg had no significant accuracy or bias compared with dosing based on BSA. A recent American Society of Clinical Oncology (ASCO) guideline for dosing in obese adult patients with cancer recommended limiting the fixed dosing of cytotoxic agents because there is insufficient evidence that fixed-dosing strategies are equivalent to weight-based or BSA-based dosing for toxicity or efficacy.[31] Therefore, further research is warranted to determine whether fixed dosing is a more appropriate strategy for treatment with docetaxel.

The present study has some limitations. The study population of 28 patients may be too small and homogeneous to accurately demonstrate the potential influence of BSA, LBM, and TBW on pharmacokinetics. Sex and tumor type seem to be important factors in docetaxel toxicity and exposure.[5,32] In addition, there are several methods for assessing body composition, such as anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), and computed tomography (CT). In this study, DEXA scans were used, which showed strong correlations between body composition parameters obtained to those obtained by CT in adults with normal weight. Obesity can cause changes in body composition, however, that may affect the assessment of fat mass and lean soft tissue mass by DEXA.[33] This study included a relatively high percentage of people who were overweight or obese, for whom CT may have been a more accurate LBM measurement. Furthermore, the CYP3A4-metabolizing capacity of the patients was not examined. In future research, it would be interesting to investigate the ability of this enzyme to metabolize exogenous substrates in patients receiving docetaxel.

CONCLUSION

This study found no clinically relevant correlations between docetaxel pharmacokinetics and the anthropometric and body composition variables BSA, LBM, and TBW. Dose individualization of docetaxel based on LBM, TBW, or fixed dosing seemed not to be superior to that based on BSA. Further comparative research is warranted between fixed and BSA-based dosing to assess the most appropriate dosing strategy.

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