Lean body mass and total body weight versus body surface area as determinant of docetaxel pharmacokinetics and toxicity

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Abstract

Aim: In our study we examined whether anthropometric and body composition parameters, i.e. body surface area (BSA), lean body mass (LBM) and total body weight (TBW), are correlated with docetaxel clearance and exposure. In addition, LBM, TBW and a fixed dose were compared to BSA as dosing parameters for dose individualisation of docetaxel. Methods: Thirty-six patients affected by breast or castration-resistant prostate carcinoma receiving docetaxel chemotherapy entered the study. LBM was measured by a Dual Energy Xray Absorptiometry (DEXA) scanner before treatment. Blood samples were collected up to 180 minutes after dosing to analyse docetaxel concentrations and to determine individual pharmacokinetic (PK) parameters. Results: No significant correlations were found between the docetaxel pharmacokinetic parameters clearance and volume of distribution and the anthropometric and body composition variables BSA, LBM and TBW. AUC was significantly but poorly correlated with BSA (r=0.452 [p=0.016]) and with TBW (r=0.476 (p=0.011]). The Mean Absolute Percentage Error and Mean Error of simulated dosing based on LBM and fixed dosing ME were not significant different compared to BSA. For TBW, only the MAPE of dosing was significant higher compared to BSA (24.1 vs. 17.1, P=0.001). Conclusion: There is no correlations between docetaxel pharmacokinetics and the anthropometric and body composition variables BSA, LBM and TBW. Dose individualisation of docetaxel based on LBM or TBW or fixed dosing cannot be recommended over BSA based dosing.

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What is already known about this subject

- Lean body mass (LBM) correlates better with drug clearance of doxorubicin, epirubicin and fluorouracil when compared to body surface area (BSA);
- Patients with comparable BSA values show a wide variety in liver volume and LBM, while liver volume is strongly correlated with LBM;
- Docetaxel is mainly metabolized by the liver.

What this study adds

No correlation was found between docetaxel clearance or exposure and BSA, LBM or total body weight (TBW);

Dose individualisation of docetaxel based on LBM or TBW cannot be recommended as an alternative for BSA based dosing.

Abstract

Aim: In our study we examined whether anthropometric and body composition parameters, i.e. body surface area (BSA), lean body mass (LBM) and total body weight (TBW), are correlated with docetaxel clearance and exposure. In addition, LBM, TBW and a fixed dose were compared to BSA as dosing parameters for dose individualisation of docetaxel.

Methods: Thirty-six patients affected by breast or castration-resistant prostate carcinoma receiving docetaxel chemotherapy entered the study. LBM was measured by a Dual Energy Xray Absorptiometry (DEXA) scanner before treatment. Blood samples were collected up to 180 minutes after dosing to analyse docetaxel concentrations and to determine individual pharmacokinetic (PK) parameters.

Results: No significant correlations were found between the docetaxel pharmacokinetic parameters clearance and volume of distribution and the anthropometric and body composition variables BSA, LBM and TBW. AUC was significantly but poorly correlated with BSA (r=0.452 [p=0.016]) and with TBW (r=0.476 (p=0.011]). The Mean Absolute Percentage Error and Mean Error of simulated dosing based on LBM and

fixed dosing ME were not significant different compared to BSA. For TBW, only the MAPE of dosing was significant higher compared to BSA (24.1 vs. 17.1, P=0.001).

Conclusion: There is no correlations between docetaxel pharmacokinetics and the anthropometric and body composition variables BSA, LBM and TBW. Dose individualisation of docetaxel based on LBM or TBW or fixed dosing cannot be recommended over BSA based dosing.

Original article

Introduction Docetaxel is a semi-synthetic taxane derivate neoplastic agent which is used in the treatment of breast and castration-resistant prostate carcinoma (CRPC), and several other cancers.[8] Pharmacokinetics of docetaxel shows a high inter-individual variability in clearance, which may result in under- or overdosing.[1] In order to reduce this variability, doses are currently based on body surface area (BSA).[2]

Dosing of anticancer drugs based on BSA is common practice since the 1950's.[3] Dosing on BSA is the method for predicting a safe starting dose in phase 1 human trials translated from animal toxicology data.[3,4] However, many argued whether this approach results in an optimal dose for each individual. BSA-based dosing has shown to result in high inter-individual variability in drug exposure for most anticancer drugs leading to undesirably side effects or insufficient tumour response. Therefore, BSA-based dosing is much debated as the method of choice for dosing chemotherapeutics.[1,5] Pharmacokinetic parameters such as clearance and area under the curve (AUC) are known markers for predicting therapeutic responses.[2] A study of Engels et al showed that the application of therapeutic drug monitoring (TDM) significantly decreased the inter-individual variability in docetaxel exposure when compared to BSA based dosing.[6] Although TDM is an elegant way of dose optimisation, it is very labour intensive and costly in the day-to-day clinical setting. Therefore, alternative anthropometric parameters that correlate better with drug exposure may be considered to optimize dosing of anticancer drugs.[7,8]

Docetaxel doses vary from 75-100 mg/m^2 given once every three weeks during an one hour intravenous infusion. Docetaxel is metabolised in the liver via oxidation by CYP3A4, CYP3A5 and is bound to albumin for 95% without significant renal clearance.[9-11] The pharmacokinetics of docetaxel can be best described by a three-compartment model with half-life times of 4.5 minutes, 38.3 minutes and 12.2 hours, respectively. The area under the plasma concentration time curve (AUC) increases proportionally with increasing doses. Docetaxel is distributed in tissues with a mean volume of distribution (VD) of 74 L/m^2.[9]Docetaxel is characterized by highly interindividual pharmacokinetic variation, with up to 10-fold differences in drug clearance in patients with normal hepatic function.[12] Bruno *et al*found a median clearance of 36.6 L/h (5th to 95th range 17.5 L/h to 59.3 L/h).[13] This variability may lead to adverse effects or to suboptimal treatment or even treatment failure. The major adverse effect is neutropenia, which is dose-limiting most of the times.[9] Other frequently occurring side effects of docetaxel are anaemia, alopecia, nausea, asthenia, peripheral neuropathy, fluid retention and nail toxicity.[10,11]

Lean body mass (LBM) could be an alternative dosing parameter to BSA, since LBM has shown to correlate better with drug clearance of cisplatin, paclitaxel and troxacitabine when compared to BSA or total body weight (TBW) in obese patients.[14] LBM as a dosing parameter has been investigated for several anticancer drugs.[7,15-23]

Patients with comparable BSA values showed a wide variety in liver volume and LBM. Since liver volume is strongly correlated with LBM and docetaxel is mainly metabolized by the liver, it is hypothesized that individual dosing on LBM should be preferred over BSA.[24,25]

In our study we examined which of the anthropometric and body composition parameters BSA, LBM and TBW correlates best with docetaxel clearance (CL) and exposure (AUC). In addition, LBM, TBW and a fixed dose were compared to BSA as dosing parameters for dose individualisation of docetaxel.

Methods *Patients and study* We performed a multi centred prospective study in patients using docetaxel. Patients that received chemotherapy with docetaxel for breast cancer or castration-resistant prostate carcinoma (CRPC) were included. Docetaxel in breast cancer treatment is part of a combined therapy with

cyclophosphamide and doxorubicin. In patients with CRPC docetaxel was given as monotherapy. Other criteria for inclusion were: absolute neutrophile count: $> 1.5\text{x}10^9$ /L, serum creatinine [?] 2x ULN, total bilirubin $<$ 1.5 ULN. Exclusion criteria were docetaxel use in the last year, moderate or severe liver impairment ([ALAT and/or ASAT [?] 1.5 ULN] and [AF [?] 2.5 ULN]), current therapy with any drug, dietary supplements, or other compounds known to inhibit or induce CYP3A4. Every patient received 75 or 100 mg/m^2 docetaxel dissolved in a saline solution and infused over one hour. Estimation of the study population size, 36 participants, was derived from studies by Gusella and Prado.[7,15] 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 in kg. A fixed stadiometer was used to determine the patients height, standing barefoot against a straight wall. LBM was measured by a DEXA-scanner. In the Deventer Teaching Hospital patients were scanned by a GE Lunar Scanner (GE healthcare, Little Chalfont; United Kingdom), while patients in Radboud University Medical Centre were scanned with a Hologic Discovery scanner (Hologic, Bedford, U.S.A.).

PK sampling and analysis Pharmacokinetic blood samples were obtained at t=0 (just prior to infusion), t=30 minutes after start of infusion, t=55 minutes after start of infusion (i.e. just prior to the end of infusion) and a last sample was obtained at t=180 minutes after start of infusion, according to a validated limited sampling strategy.[26-28]Docetaxel plasma concentrations were quantified using a HPLC-UV method. First liquid-liquid extraction was performed with tert-butylmethylether as extraction fluid/organic layer. The plasma layer is frozen on a cryo bath and the organic layer is evaporated with compressed air. HPLC-UV analysis was done with paclitaxel as internal standard. Methanol/phosphate buffer (65:35 v:v) was used as mobile phase, flow: 1.0 mL/min, detection 230 nm. The method was validated in line with the European Medicines Agency Guideline on bioanalytical validation.[29] NONMEM$^{(r)}$ software (ICON, Ireland) was used to determine the individual clearance (CL) and distribution volume (Vd) by Bayesian analysis using a population model described by Engels et al.[6] The area under the curve (AUC) was calculated with the formula:

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

Biochemical parameters

As a part of standard hospital protocol haematology and biochemistry assessments were done before every chemo course: aminotransferase (ASAT), alanine-amino transferase (ALAT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), alpha-1-acidglycoprotein (AAG), albumin (ALB), total bilirubin, creatinine, haemoglobin (Hb), hematocrit (Ht), red cell count (RBC), platelat count, total white cell count (WBC) and diffferential white cell count.

Data and statistical analysis Data were expressed as median with their interquartile range (IQR). Comparison between median values obtained in females and males were made using the Mann-Whitney U test for unpaired data. The accepted significance level was $p<0.05$. Linear regression analysis was used to compare correlations of BSA, LBM and TBW with docetaxel clearance and exposure. Correlations were therefore evaluated by determining Spearman correlation coefficients with corresponding p values.

Different doses were simulated, based on individual anthropometric and body composition parameters and median docetaxel/BSA, docetaxel/LBM, docetaxel/TBW and docetaxel dose (referred as fixed dose). An 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 mean absolute percentage error (MAPE):

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

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

Bias was calculated using the mean error (ME):

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

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

Toxicity Toxicity due to chemotherapy was scored by the physicians during all treatment cycles according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 criteria.[30] Only grade 3 and 4 toxicities were considered in the analysis. Premature therapy termination (patient does not complete the standard 6 or 10 cycles), dose delay (patient needs more than 3 weeks to recover from chemotherapy) and dose reduction because of toxicity, were recorded. Overall toxicity was defined when; any toxicity [?] grade 3, and/or dose delay, dose reduction and premature treatment termination occurred due to toxicity.

Results

A total of 36 patients, of which 28 were female, were included in the Deventer Teaching Hospital (n=20) and Radboud University Medical Centre (n=16). Docetaxel data of eight subjects were not evaluated: in six patients blood was taken in the infusion arm and two patients refrained from blood sampling. Another two patients were lost to follow-up for toxicity data. Figure 1 shows a flowchart of the included patients.

Patient characteristics, the main demographic, anthropometric, body composition and docetaxel pharmacokinetic parameters in males, females, and in the whole study population are shown in Table 1. Females had significantly lower median age when compared with males (56 [12.9] vs. 69.6 [16.3], p = 0.024). This is probably because docetaxel is given primarily for women with breast cancer which are mostly diagnosed at a younger age than CRPC in men. Another significant difference concern a lower LBM of females than of men (45.7 [8.4] vs. 54.5 [7.7], p = 0.017) in accordance with literature data.[16,31] None of the pharmacokinetic parameters differed between males and females, except for dose (females 140 [20] vs. males 160 [18], p = 0.040) and dose/LBM (females 3.09 [0.3] vs. males 2.80 [0.2], p=0.020).

Correlation of anthropometric and body composition parameters

No significant correlations were found over the whole population between the docetaxel pharmacokinetic parameters clearance and volume of distribution and the anthropometric and body composition variables BSA, LBM and TBW. AUC was significant but poor correlated with BSA and TBW, Table 2; Figure 2.

Simulation of dosing methods

Results of the simulated dosing methods based on median BSA, LBM, TBW and fixed dosing are presented in Table 3 and visualized in Figure 3. The optimal target AUC was calculated and resulted in an AUC of 3.13 mg.h/L. For evaluation of the simulated doses, MAPE for accuracy and ME for bias were calculated and showed in Table 3. The MAPE and ME of simulated dosing based on LBM, TBW or fixed dosing ME were not significant different compared to BSA. Except for the MAPE of dosing based on TBW, which was significant higher compared to BSA (p=0.001).

Toxicity correlations

The incidence of severe toxicity (i.e. [?] grade 3) is shown in Table 4. One patient experienced grade 3 mucositis, five patients experienced grade 3 or 4 neutropenia and six patients had other forms of toxicity (fatigue, febrile neutropenia, hyperglycaemia, infection, leucopenia, and polyneuropathy). No significant relationships 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 were found.

Discussion

To our knowledge this is the first study that examines relationships between the pharmacokinetics of docetaxel and the anthropometric and body composition parameters BSA, LBM and TBW. No correlations were found between clearance or volume of distribution of docetaxel and the anthropometric and body composition parameters BSA, LBM and TBW. Exposure (AUC) was significantly but poorly correlated with BSA and TBW with a Spearman correlation coefficient of 0.452 (p=0.016) and 0.476 (p=0.011), respectively. Besides, we found that docetaxel dosing based on LBM and TBW or fixed dosing appeared not to be superior to BSA after simulated dosing.

Over the last two decades, there has been an increase in the number and homogeneity of studies published who suggested a correlation in body composition parameters other than BSA with chemotherapy pharmacokinetics and toxicity.[7,15-23] One example is a study with 1,206 adult cancer patients of whom 162 were obese (body mass index [?]30) in which the absolute clearance of cisplatin, paclitaxel, and troxacitabine was significantly higher in the obese. For docetaxel and doxorubicin, the authors concluded that applying LBM as a dosing scalar seems to be of particular merit.[16] Our study included nine obese patients (32.1%), in which we could not find a significant correlation between any of the anthropometric or body composition parameters and docetaxel pharmacokinetics. Another study correlated LBM with epirubicin log-clearance with a Pearson's correlation of 0.43.[17]Our study found significant Spearman's correlations of 0.45 and 0.48 for BSA and TBW with docetaxel AUC, respectively. In contrast to the epirubicin study, we did not apply the variable in a systematic multivariable model.

Several other studies highlighted the difference 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.[20-23]In our study there was no trend of a higher docetaxel/BSA, docetaxel/LBM or docetaxel/TBW in patients that experienced overall toxicity compared to patients who did not. In our study nine patients experienced severe toxicity, that resulted for seven of them in dose delay, reduction or termination of treatment. Five patients experienced grade 3 or 4 neutropenia, which is lower than in other studies.[26]

In contrast to most of the other studies, no correlations were found between clearance of docetaxel and the parameters BSA, LBM and TBW. As a consequence, our results do not support the application of any of these parameters for individualisation of docetaxel therapy. This includes BSA, which is widely used in daily practise for this purpose. In our dosing simulation, a fixed dosing method was also executed. Strikingly, a fixed dose of 140 mg had no significant other accuracy or bias compared to dosing based on BSA. A recent ASCO guideline for dosing for obese adult patient with cancer recommend to limit fixed dosing of cytotoxic agents since there is insufficient evidence that fixed-dosing strategies are equivalent to weight- or BSA-based dosing in terms of toxicity and efficacy.[32] Therefore, further research is warranted to determine whether fixed dosing is a more appropriate strategy for treatment with docetaxel.

Our study had some limitations. The study population with 28 patients might be too small and too homogeneous to demonstrate the potential influence of BSA, LBM and TBW on pharmacokinetics. Gender and tumour type seems to be an important factor in docetaxel toxicity and exposure.[7,33] In addition, there are several methods for assessing body composition available such as anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT). In our study we used DEXA scans which have shown strong correlations between body composition parameters obtained by DEXA and those obtained by CT in adults of normal weight. However, obesity can cause changes in body composition that may impact the assessment of fat mass and lean soft tissue mass by DEXA.[34] Our study included a relatively high percentage of people with overweight or obesity, for whom a CT may have been a more accurate measurement to determine LBM. Furthermore, the CYP3A4 metabolizing capacity of patients was not examined. In future research it could be interesting to investigate the ability to metabolize exogenous substrates by this enzyme in patients who receive docetaxel.

Conclusion

Our study shows no correlations between docetaxel pharmacokinetics and the anthropometric and body

composition variables BSA, LBM and TBW. Dose individualisation of docetaxel based on LBM or TBW or fixed dosing appeared not to be superior to BSA. Further comparative research is warranted between fixed dosing and BSA based dosing to assess the most appropriate dosing strategy.

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Conflict of interest statement

H.L. Hoge, S.E.H. Detert Oude Weme, W.L. Vervenne, I.R.F. van Berlo-van de Laar, C.M.L. van Herpen, L. Roorda, R.A.A. Mathôt, M.S. Jacobs, N.P. van Erp and F.G.A. Jansman have no conflicts of interest that are directly relevant to the content of this study.

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Data availability statement

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

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