Received: 17 September 2021 | Revised: 1 December 2021 | Accepted: 1 January 2022

DOI: 10.1111/bcp.15244

ORIGINAL ARTICLE

Muscle mass affects paclitaxel systemic exposure and may inform personalized paclitaxel dosing

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Funding information
National Cancer Institute, Grant/Award Numbers: P30CA046592, NCI U01 CA230669; National Center for Advancing Translation Sciences, Grant/Award Numbers: KL2TR000434, 2UL1TR000433; Agency for Healthcare Research and Quality (AHRQ), Grant/Award Number: R01 HS027183

Aims: Patients with low muscle mass have increased risk of paclitaxel-induced peripheral neuropathy, which is dependent on systemic paclitaxel exposure. Dose optimization may be feasible through the secondary use of radiologic data for body composition. The objective of this study was to interrogate morphomic parameters as predictors of paclitaxel pharmacokinetics to identify alternative dosing strategies that may improve treatment outcomes.

Methods: This was a secondary analysis of female patients with breast cancer scheduled to receive 80 mg/m^2 weekly paclitaxel infusions. Paclitaxel was measured at the end of initial infusion to estimate maximum concentration (C_{max}). Computed tomography (CT) scans were used to measure 29 body composition features for inclusion in pharmacokinetic modelling. Monte Carlo simulations were performed to identify infusion durations that limit the probability of exceeding C_{max} > 2885 ng/mL, which was selected based on prior work linking this to an unacceptable risk of peripheral neuropathy.

Results: Thirty-nine patients were included in the analysis. The optimal model was a two-compartment pharmacokinetic model with T11 skeletal muscle area as a covariate of paclitaxel volume of distribution (Vd). Simulations suggest that extending infusion of the standard paclitaxel dose from 1 hour to 2 and 3 hours in patients who have skeletal muscle area 4907–7080 mm^2 and <4907 mm^2, respectively, would limit risk of C_{max} > 2885 ng/mL to <50%, consequently reducing neuropathy, while marginally increasing overall systemic paclitaxel exposure.

Conclusion: Extending paclitaxel infusion duration in ~25% of patients who have low skeletal muscle area is predicted to reduce peripheral neuropathy while maintaining systemic exposure, suggesting that personalizing paclitaxel dosing based on body composition may improve treatment outcomes.

KEYWORDS
modelling and simulation, morphomics, muscle mass, paclitaxel, peripheral neuropathy, pharmacokinetics, sarcopenia, therapeutic drug monitoring

1 | INTRODUCTION

Paclitaxel is a chemotherapeutic agent commonly used for treatment of several solid tumour types including breast, lung and ovarian cancer. Like most chemotherapy agents, paclitaxel is dosed based on body surface area (BSA),[1] including the 1-hour 80 mg/m^2 weekly or 3-hour 175 mg/m^2 every two- or three-week standard regimens for breast cancer.[2,3] These "maximum tolerated doses" are believed to maximize efficacy while maintaining an acceptable risk of severe toxicity. In the case of weekly paclitaxel, the dose limiting toxicity is peripheral neuropathy (PN), which is characterized by numbness, tingling, pain and/or loss of function in the hands and feet.[4] During a pivotal phase III clinical trial of weekly paclitaxel for breast cancer, the protocol doses were revised from 100 mg/m^2 to 80 mg/m^2 weekly due to a determination that the 30% incidence of severe (grade 3+) PN was unacceptable but 24% incidence was acceptable.[3] The ~25% incidence of severe PN from weekly 1-hour infusions of 80 mg/m^2, which is the standard weekly dose used in clinical practice, can be inferred to be the maximally acceptable rate of severe or treatment-limiting toxicity.[5,6]

There has been substantial effort to identify predictors of chemotherapy-induced PN[7] that could inform personalized treatment.[8] Perhaps the most well-validated predictor of paclitaxel-induced PN is systemic paclitaxel concentrations, or pharmacokinetics (PK) (see table 1 in Ref. 9). Several studies of patients receiving weekly paclitaxel have found that higher maximum concentration at the end of infusion (C_{max}) or longer duration of systemic concentration remaining above 0.05 μM (equivalent to 42.7 ng/mL, $T_{c>0.05}$) are associated with increased PN risk.[10–12] One analysis of patients receiving weekly paclitaxel ($n = 141$) found that patients with grade 3 PN had significantly higher C_{max} (4370 ng/mL) and $T_{c>0.05}$ (15.2 h) compared with patients who had grades 0/1 PN (C_{max}: 1394–2896 ng/mL, $T_{c>0.05}$: 7.6–12.9 h).[11] Simulations in the UMCC2014.002 cohort ($n = 60$) determined the optimal systemic paclitaxel exposures that are associated with maximally acceptable (~25%) risk of treatment-limiting PN in patients receiving weekly paclitaxel are $C_{max} = 2885$ ng/mL and $T_{c>0.05} = 14.06$ hours.[10] Every standard deviation increase in C_{max} or $T_{c>0.05}$ increased the risk of treatment-limiting PN by 174% and 79%, respectively. Randomized controlled trials in patients with lung cancer receiving every 3-week paclitaxel demonstrate that personalized paclitaxel dosing to achieve a target $T_{c>0.05}$ reduces PN and overall toxicity without reducing efficacy.[13,14]

Another biomarker that has been repeatedly found to increase chemotherapy toxicity risk is low muscle mass, or sarcopenia (reviewed in Ref. 15). Sarcopenic patients have higher incidence of toxicity from paclitaxel[16] as well as higher PN risk from oxaliplatin,[17] another neurotoxic chemotherapy agent. Although muscle mass has been reported to affect PK of some chemotherapeutic drugs,[15,18–21] a recent study did not detect an effect on paclitaxel PK.[22] If sarcopenia affects paclitaxel PK and consequently increases PN risk, it may be possible to personalize dosing based on muscle mass to reduce PN and improve paclitaxel treatment outcomes.

What is already known about this subject

- Patients with low muscle mass (i.e., sarcopenia) have increased risk of toxicity from chemotherapy, including paclitaxel-induced peripheral neuropathy.
- Paclitaxel-induced peripheral neuropathy is primarily dependent on systemic paclitaxel exposure.
- Low muscle mass increases systemic exposure of some chemotherapeutic agents, but its effect on paclitaxel is not established.

What this study adds

- Low muscle mass increases paclitaxel maximum concentration by decreasing volume of distribution.
- This likely explains the higher incidence of paclitaxel toxicity.
- Extending the paclitaxel infusion in patients with low muscle mass is expected to normalize their maximum concentration and may reduce peripheral neuropathy.

Patients with breast cancer often undergo radiologic assessments such as computed tomography (CT) and magnetic resonance imaging (MRI) to assess disease stage or monitor disease progression. Innovative methods have been developed to translate existing CT data into body composition metrics, a discipline known as morphomics.[23,24] Quantitative body composition data derived from existing CT data may deliver a useful stratification tool that can improve paclitaxel safety through personalized dosing. The objective of this study was to perform PK modelling and simulation in the UMCC2014.002 cohort to compare the current BSA dosing standard to new morphomic metrics PK and propose personalized weekly paclitaxel dosing strategies that could reduce PN without compromising efficacy.

2 | METHODS

2.1 | Patients and pharmacokinetic data

This was a secondary PK analysis of participants who were previously described in detail.[10] Briefly, adult female patients scheduled to receive 1-hour infusions of 80 mg/m^2 paclitaxel weekly for 12 weeks for curative breast cancer treatment at the University of Michigan Rogel Cancer Center were enrolled on an observational clinical trial (NCT02338115) before their first paclitaxel dose. This study was approved by the University of Michigan IRBMed (HUM00086259) and was conducted in accordance with the Declaration of Helsinki including obtaining written informed consent from all participants. D.L.H. was the principal investigator and N.L.H. was the primary

clinical investigator of the observational trial. Paclitaxel dosing was administered according to the Rogel Cancer Center's standard protocol, including use of actual body weight to calculate BSA, administration of standard pre-treatment medications and infusing the first dose over 90 minutes to monitor for infusion reactions.

Sample collection and paclitaxel concentration measurement were previously described in detail.[10] Briefly, blood samples were collected within the last 10 minutes of the first paclitaxel infusion to estimate the maximum concentration (C_{max}) and 16–26 hours after the start of the first paclitaxel infusion to estimate the amount of time the patient's systemic concentration remained above 0.05 μM (or 42.7 ng/mL, $T_{c>0.05}$).[25] All samples were immediately placed on ice and processed within 10 minutes of collection to isolate plasma. Paclitaxel plasma concentration was measured by the University of Michigan College of Pharmacy Pharmacokinetics Core using a liquid chromatography/mass spectroscopy assay that enables quantitation of paclitaxel concentrations over the linear range of 5–5000 ng/mL (additional details of paclitaxel assay performance can be found in the **Supplementary Methods** available online).[10]

2.2 | Imaging data cleaning

The University of Michigan electronic medical record (MiChart) was queried for all CT scans for all observational study participants. Only CT scans that occurred within 12 months of the date of first paclitaxel infusion were included in the analysis. CT scans were processed using analytic morphomics to estimate 29 unique parameters (Table S1) at each of the seven vertebral levels (e.g., Lumbar 1–4, Thoracic 10–12), as previously described.[23,24]

2.3 | Paclitaxel pharmacokinetic modelling

Population PK analysis was performed using Monolix Version 2020R1 (Antony, France: Lixoft SAS, 2020). Briefly, a one- and two-compartment model with zero-order input, elimination and transfer-rate constants were tested to select the base structural model. The presence of a large number of potential covariates (~200 morphomic parameters) and clinical covariates (age, race, BSA, albumin) required use of the automated covariate building algorithms in Monolix.[26] We tested both the conditional sampling use for stepwise approach based on correlations (COSSAC) test as well as the classic stepwise covariate modelling (SCM) method at one vertebral level to identify the principal covariates (Figure S1). Although more time-intensive, the SCM method was selected for all other vertebral levels based on the model fits. Next, we identified the vertebral level that best fit the data with a covariate structured model. For fair comparison of likelihood results, we limited the study sample to participants with the same amount of information at each vertebral level. A manual stepwise covariate model approach was used to create the most parsimonious model to aid future clinical implementation. We evaluated both a rate constant (V, k, k12, K21) and clearance parameterized (CL, V1, Q, V2) structural model. The final model structure was then used to fit all available data at that vertebral level to generate the base (no covariate), BSA-structured and morphomics-structured model. We also tested additive, proportional and combined residual error models. Model discrimination was based on the Akaike information criterion (AIC), with diagnostic evaluation of the non-parametric distributional error (NPDE), individual weighted residuals and other goodness-of-fit plots.

2.4 | Simulations of infusion duration to prevent peripheral neuropathy

The final population PK model was evoked in Simulx Version2020R1 (Antony, France: Lixoft SAS, 2020) and used to simulate the concentration–time profile of paclitaxel 80 mg/m^2 infused over 1, 2 and 3 hours. The simulations ($n = 1000$ virtual subjects) were based on the principal covariate predictive of the PK and performed at stepwise values across the expected distribution of this covariate in the population. The probability of achieving a $C_{max} \geq 2885$ ng/mL or $T_{c>0.05} \geq 14.06$ hours was computed for each dose and covariate simulation, as our prior work in this cohort indicates that these values are the exposures associated with maximally acceptable (25%) risk of treatment-limiting PN.[10] A scatter plot of the probability of achieving the aforementioned pharmacodynamic targets over the SMA were generated and fit using nonlinear regression in Stata SE version 17 (StataCorp LLC, College Station, TX, USA). A logistic function (symmetric sigmoid shape) with no constant [probability of target attainment $= \beta_1/(1 + \exp(-\beta_2 \times [\text{SMA-}\ \beta_3]))$] best fit these relationships and was used to identify cut-off points at the 50% probability of pharmacodynamic target attainment for the C_{max} or $T_{c>0.05}$ parameter.

3 | RESULTS

3.1 | Patients, pharmacokinetic and morphomic data

Of the 60 patients included in the observational clinical study, 57 had paclitaxel measurements available at both time points. Of these 57 patients, CT scans within 1 year were available for 39 patients, all of which generated morphomics measurements at Thoracic 11 (T11) (Figure 1). Similar to the overall cohort, participants were mostly White (90%) with a mean age of 50 and BSA of 1.8 m^2 (Table 1).

3.2 | Paclitaxel pharmacokinetic modelling

The models identified by SCM at each vertebral level included various combinations of one clinical (albumin) and nine morphomics covariates (Table S2 and Figure S2). The best model at any

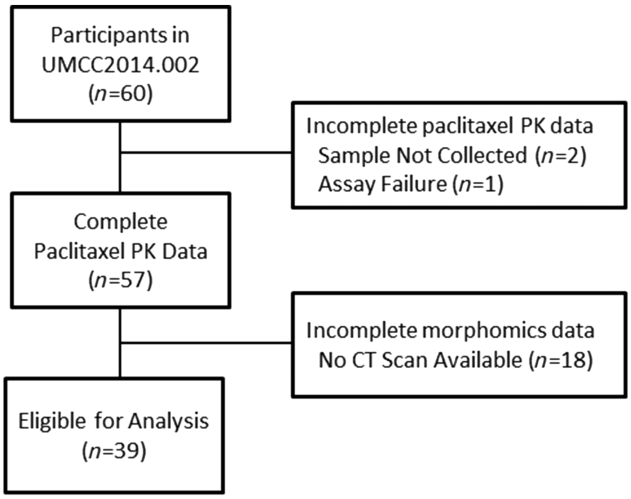

FIGURE 1 Patient flow diagram describing patient matriculation from initial observational study in this analysis. Of the 60 patients in the observational study, 39 were evaluable in this analysis based on complete paclitaxel pharmacokinetic data and CT scans available to generate morphomics measures at T11

vertebral level included three morphomics measurements: skeletal muscle area (SMA) and visceral fat area (VFA) as covariates on volume of distribution (Vd) and vertebra slab height (VSH) as a covariate on elimination rate constant (k), from T11 and no clinical covariates. Further model exploration at T11 indicates that there is minimal benefit from including all ten or three covariates, compared with a more parsimonious model with a single covariate (Tables S3 and S4). Models with SMA had lower AIC values compared to models that did not include this parameter. The CL structured model had lower AIC values than the k-structured models. In comparison with the base (no covariates) and BSA-structured model, the morphomic model including SMA has a lower AIC with clear improvement in the relative standard error of the random effect terms (Table 2 and Table S5). This final morphomic model with only SMA as a covariate of volume of distribution (central and peripheral) has a >2-point (6.4-point) difference in AIC compared to the BSA-structured model, which is regarded as a substantive difference.[27] Model diagnostics and performance are provided in Figures S3–S6.

TABLE 1 Patient, treatment and morphomics data for patients included in the analysis ($n = 39$)

		n or mean	% or range
Age	Years	50	28 to 71
Self-reported race	White	35	90%
	African American	2	5%
	Asian	2	5%
Weight	kg	71	48 to 134
Height	meters	1.63	1.55 to 1.78
Albumin	g/dL	4.0	2.0 to 4.5
Infusion duration	90 minutes	38	97%
	180 minutes	1	3%
Vertebral level with available morphomics data	Thoracic 10 (T10)	37	95%
	Thoracic 11 (T11)	39	100%
	Thoracic 12 (T12)	36	92%
	Lumbar 1 (L1)	33	85%
	Lumbar 2 (L2)	32	82%
	Lumbar 3 (L3)	32	82%
	Lumbar 4 (L4)	32	82%
Morphomics measures at T11	Skeletal muscle area (mm^2)	8382	4825 to 11 732
	Visceral fat area (mm^2)	5979	613 to 17 341
	Subcutaneous fat area (mm^2)	13 576	2325 to 35 036
	Height of slab at vertebra (mm)	28.3	25.0 to 32.7
	Skeletal muscle density (HU)	41.4	28.4 to 53.7
	Visceral fat density (HU)	−95.9	−107 to −84.7
	Subcutaneous fat density (HU)	−103	−112 to −89.3

Abbreviation: HU, Hounsfield units.

TABLE 2 Comparison of the population pharmacokinetic parameters of the base model, body surface area (BSA) model and morphomic model (selected as the final model)

	Base model AIC = 849.02			BSA model AIC = 834.92			Morphomic model AIC = 828.52		
	Value	SE	RSE (%)	Value	SE	RSE (%)	Value	SE	RSE (%)
Fixed effects									
Cl_pop	29.77	6.7	22.5	20.16	1.91	9.49	18.43	0.52	2.85
V1_pop	28.55	8.33	29.2	41.52	2.88	6.93	43.51	2.59	5.95
θ_1	N/A	N/A	N/A	1.64	0.47	28.6	N/A	N/A	N/A
θ_2	N/A	N/A	N/A	N/A	N/A	N/A	1.09	0.3	27.4
Q_pop	0.313	0.106	33.7	3.66	0.44	12	3.15	0.26	8.19
V2_pop	0.336	0.138	41.1	115.2	13.33	11.6	109.62	12.51	11.4
θ_3	N/A	N/A	N/A	3.12	0.56	17.9	N/A	N/A	N/A
θ_4	N/A	N/A	N/A	N/A	N/A	N/A	2.22	0.25	11.2
Standard deviation of the random effects									
omega_Cl	0.14	0.044	30.7	0.075	0.094	125	0.046	0.032	71.1
omega_V1	0.45	0.52	115	0.21	0.075	35.7	0.19	0.067	36
omega_Q	0.093	0.25	269	0.076	0.029	38.2	0.097	0.045	46.1
omega_V2	0.23	0.34	145	0.12	0.091	77.3	0.098	0.12	122
Error model parameters									
b	0.19	0.11	56	0.21	0.065	31.4	0.21	0.031	15

Abbreviations: SE, standard error; RSE, relative standard error; AIC, Akaike information criterion.
$V1 = V1\_pop \times (BSA/1.87)^{\theta 1}$.
$V1 = V1\_pop \times (SMA/8000)^{\theta 2}$.
$V2 = V2\_pop \times (BSA/1.87)^{\theta 3}$.
$V2 = V2\_pop \times (SMA/8000)^{\theta 4}$.
b = proportional error term.

3.3 | Identification of optimal infusion duration to prevent peripheral neuropathy

The final PK model was used in simulations to identify optimal infusion durations for patients with varying SMA (4000–12 000 mm^2 in increments of 1000 mm^2). Since the main effect of SMA was on Vd, not elimination rate (k), simulations focused on the threshold of $C_{max} \geq 2885$ ng/mL. The simulation was conducted to identify ranges of SMA for which infusion durations should be increased from 1 hour to 2 and 3 hours to retain <50% chance of $C_{max} \geq 2885$ ng/mL. Based on this threshold, patients with SMA > 7080 mm^2 should receive the standard 1-hour paclitaxel infusion, those with SMA 4907–7080 mm^2 should receive a 2-hour infusion and those with SMA < 4907 mm^2 should receive a 3-hour infusion (Figure 2). These thresholds correspond to approximately 2% (skeletal muscle area <4907 mm^2) and 15% (4907–7080 mm^2) of 50-year-old (median in our cohort) female patients.[23] Extending the infusion duration marginally increases overall exposure and $T_{c>0.05}$; less than 25% of patients receiving these recommended infusion durations exceed the threshold $T_{c>0.05} > 14.06$ (Figure S7).

4 | DISCUSSION

Patients with sarcopenia have increased toxicity risk from many chemotherapy drugs,[15–17,28–31] including paclitaxel.[16] Paclitaxel-induced PN is primarily determined by systemic paclitaxel exposure, including maximum concentration.[10,11] Although sarcopenia affects PK of some chemotherapy agents,[15,18–21] an effect on paclitaxel PK has not previously been detected.[22] The results of this secondary PK analysis of a prospectively enrolled cohort of patients receiving paclitaxel indicate that lower muscle mass increases maximum paclitaxel concentration, with minimal effect on overall exposure, and that extending paclitaxel infusions to 2 or 3 hours in patients with low muscle mass may reduce PN while maintaining treatment efficacy.

A retrospective analysis of 40 patients receiving taxanes for metastatic breast cancer found that the sarcopenic patients ($n = 23$) experienced greater incidence of grade 3–4 toxicity (57% *vs.* 18%, $P = .02$) and hospitalization (39% *vs.* 0%, $P = .005$).[16] Additionally, analyses of two cohorts of patients with metastatic colorectal cancer receiving combination chemotherapy containing neurotoxic oxaliplatin demonstrate that sarcopenia increases risk of chemotherapy-induced PN.[17] Although

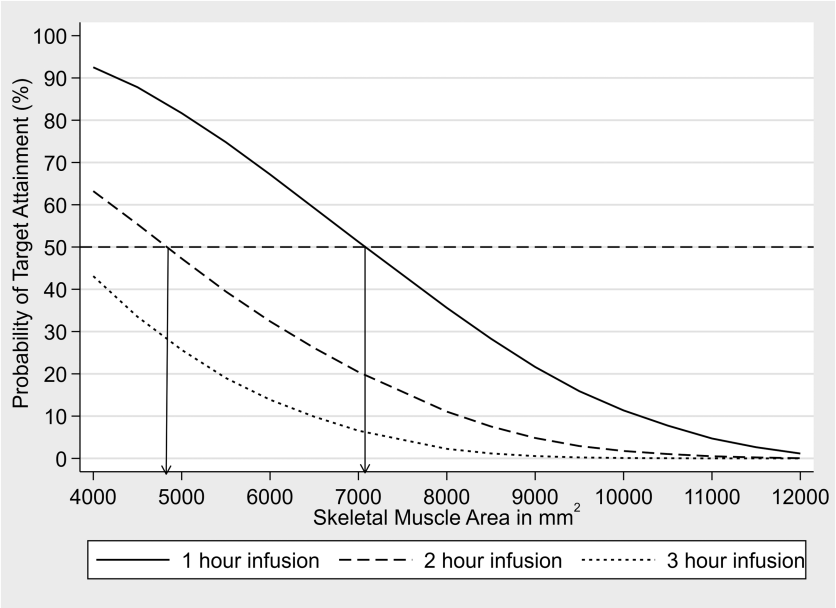

FIGURE 2 Infusion duration to prevent supratherapeutic paclitaxel dosing. The relationship between skeletal muscle area (mm^2, *x*-axis) and risk of supratherapeutic exposure ($C_{max} \geq 2885$) is plotted for a 1-hour (solid line), 2-hour (hatched line), and 3-hour (dotted line) infusion of paclitaxel 80 mg/m^2. Patients with skeletal muscle area <7080 and <4907 mm^2 should receive a 2-hour and 3-hour infusion, respectively, to reduce their risk of supratherapeutic exposure and peripheral neuropathy

these are mostly small retrospective studies with varying definitions of body composition and toxicity, the consistent finding that sarcopenia increases toxicity risk strongly suggests this is a real phenomenon. Among several potential mechanistic explanations, perhaps the most likely is that body composition affects systemic chemotherapy exposure, which has been demonstrated for several chemotherapeutic agents.[15,18–21] However, a recent analysis in 184 patients with oesophageal cancer found that skeletal muscle or adipose tissue measures were not superior to BSA in explaining paclitaxel PK, specifically the paclitaxel metabolic elimination rate (VM_{EL}).[22] This is consistent with our results indicating that muscle mass affects paclitaxel volume of distribution, and consequently maximum concentration, but not clearance. Systematic reviews of the effect of body composition, specifically the weight-loss condition cachexia, reveal unpredictable effects on drug PK with various putative mechanisms.[32] The effect of sarcopenia on increasing maximum concentration may be a direct effect on paclitaxel distribution or a secondary effect on changes in protein binding, as paclitaxel is highly bound to albumin and alpha 1-acid glycoprotein.[33] Albumin was one of ten initially identified covariates in this analysis (Table S2) but it was not retained in later models, and further analyses to understand the complex interplay between albumin, morphomics and paclitaxel PK are not possible in this modestly sized cohort.

ASCO guidelines recommend that actual body weight be used when calculating doses for BSA-based dosing in obese patients.[1] However, there is evidence that patients with higher body mass index receive less benefit from BSA-based taxane dosing,[34] indicating that taxane dose optimization could improve treatment outcomes. Several strategies for personalized paclitaxel treatment have been suggested.[8] The most intensively pursued strategy is therapeutic drug monitoring (TDM), in which systemic paclitaxel concentrations are measured during treatment to inform personalized dose adjustments to achieve target systemic exposure. Two prospective randomized clinical trials have demonstrated that paclitaxel TDM reduces toxicity without reducing efficacy.[13,14] However, there has been minimal clinical uptake of paclitaxel TDM, which may be due to the general lack of familiarity or acceptance of TDM in oncology.[35] Another possible explanation is a concern, both from medical oncologists and patients,[36] that reducing paclitaxel doses could reduce treatment efficacy. Our simulations suggest an approach that would not require drug concentration measurement or dose reduction, but would instead recommend that about one in six patients with early-stage breast cancer with lower muscle mass receive an extended 2- or 3-hour infusion of 80 mg/m^2 instead of the standard 1-hour infusion. This approach would maintain full paclitaxel dosing and, based on our simulation, minimally increase overall time above a threshold concentration ($T_{c>0.05}$), which should, if anything, slightly enhance treatment efficacy. The inconvenience and cost of extended infusion time would likely be worth the avoidance of PN and its long-term effects on quality of life.[37,38] PN reduction would also avoid paclitaxel treatment disruption,[5,39] potentially enhancing the number of full doses that can be administered and efficacy.[30,40] Prospective studies are being developed to demonstrate that muscle mass-based dosing reduces supra-therapeutic exposure and PN, while maintaining or perhaps improving treatment efficacy.

This study demonstrates an effect of low muscle mass on paclitaxel systemic exposure. This analysis was conducted in a cohort of prospectively accrued patients with systematically collected PK data. We integrated contemporary body composition analysis within PK modelling to identify the association, followed by simulation to propose personalized infusion durations that could reduce toxicity while maintaining full dosing and treatment efficacy. However, this analysis had several limitations that are worth considering. First, this study was conducted in a modestly sized cohort ($n = 39$) with only two paclitaxel concentration measurements during the first paclitaxel infusion and used available CT scans. Larger retrospective studies could be useful to confirm the effect of sarcopenia on maximum systemic concentration prior to prospective interventional studies of personalized dosing. Using CT scans up to 12 months prior to treatment may have also introduced some variability as they may not accurately represent the patient's body composition at the time of treatment. Additionally,

the PK thresholds used in this study have not been validated. Regardless of whether these are the optimal PK thresholds, our results strongly indicate a biologically plausible effect of muscle mass on paclitaxel C_{max} and provide thresholds for prospective studies that attempt to normalize PK and toxicity risk in sarcopenic patients. We acknowledge the possibility that C_{max} is not causally related to PN and that these prospective trials will fail to demonstrate a clinical benefit to extended infusion duration. Clinical use of this strategy would require CT scans prior to dosing, which may limit this approach to only patients receiving treatment in the metastatic or high-risk adjuvant setting. Low-risk patients who do not have an available CT scan would require a CT scan, with or without contrast,[41] or muscle area measurement via another modality including MRI, bio-electrical impedance analysis or panoramic ultrasound.

In conclusion, this secondary PK analysis demonstrates that sarcopenia increases maximum systemic paclitaxel concentration, which likely explains the increased PN risk in paclitaxel-treated patients. Simulations indicate that extending infusion by 1–2 hours in the ~17% of patients with the lowest muscle mass may reduce supra-therapeutic exposure and PN. Prospective studies are needed to demonstrate that this approach improves paclitaxel treatment outcomes prior to translation into clinical practice.

ACKNOWLEDGEMENTS

This research was funded in part by the National Center for Advancing Translation Sciences (NCATS 2UL1TR000433, KL2TR000434) (DLH), Agency for Healthcare Research and Quality (AHRQ R01 HS027183) and National Cancer Institute (NCI U01 CA230669 and P30CA046592) through use of the UM Morphomics Analysis Group and Pharmacokinetics Core. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, AHRQ, NCATS, or NCI.

COMPETING INTERESTS

D.L.H. has an informal, unpaid collaborative relationship with Saladax Inc., a company that offers CLIA-approved paclitaxel measurement. Saladax was not involved in the design, conduct, analysis or sponsorship of this trial, and had no contribution to the writing of this manuscript. S.C.W. owns equity in Prenovo, Applied Morphomics, Inc. and EIQ, none of which were involved in this research.

CONTRIBUTORS

D.L.H. designed and oversaw clinical study, designed and oversaw analysis and wrote the manuscript; L.C. collected the radiologic and clinical data, assisted pharmacokinetic analysis and reviewed the manuscript; N.L.H., J.J.G. and D.F.H. enrolled participants and reviewed the manuscript; B.A.D., G.L.S. and S.C.W. analysed the radiologic data, estimated body composition and reviewed the manuscript; M.P.P. conducted pharmacokinetic analysis and reviewed the manuscript.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request to the corresponding author.

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REFERENCES

1. Griggs JJ, Bohlke K, Balaban EP, et al. Appropriate systemic therapy dosing for obese adult patients with cancer: ASCO Guideline update. *J Clin Oncol*. 2021;39(18):2037-2048. doi:10.1200/JCO.21.00471
2. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. *J Clin Oncol*. 2015;33(1):58-64. doi:10.1200/jco.2014.56.3296
3. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B Protocol 9840. *J Clin Oncol*. 2008;26(10):1642-1649. doi:10.1200/JCO.2007.11.6699
4. Rowinsky EK, Chaudhry V, Cornblath DR, Donehower RC. Neurotoxicity of taxol. *J National Cancer Inst Monogr*. 1993;15(15):107-115.
5. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO Guideline update. *J Clin Oncol*. 2020;14(10):01399. doi:10.1200/JCO.20.01399
6. Speck RM, Sammel MD, Farrar JT, et al. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in non-metastatic breast cancer. *J Oncol Pract*. 2013;9(5):e234-e240. doi:10.1200/jop.2012.000863
7. Chan A, Hertz DL, Morales M, et al. Biological predictors of chemotherapy-induced peripheral neuropathy (CIPN): MASCC neurological complications working group overview. *Support Care Cancer*. 2019;27(10):3729-3737. doi:10.1007/s00520-019-04987-8
8. Krens SD, McLeod HL, Hertz DL. Pharmacogenetics, enzyme probes and therapeutic drug monitoring as potential tools for individualizing taxane therapy. *Pharmacogenomics*. 2013;14(5):555-574. doi:10.2217/pgs.13.33
9. Hertz DL. Exploring pharmacogenetics of paclitaxel- and docetaxel-induced peripheral neuropathy by evaluating the direct pharmacogenetic-pharmacokinetic and pharmacokinetic-neuropathy relationships. *Expert Opin Drug Metab Toxicol*. 2021;6(2):1-13. doi:10.1080/17425255.2021.1856367
10. Hertz DL, Kidwell KM, Vangipuram K, et al. Paclitaxel plasma concentration after the first infusion predicts treatment-limiting peripheral neuropathy. *Clin Cancer Res*. 2018;24(15):3602-3610. doi:10.1158/1078-0432.ccr-18-0656
11. de Graan A-JM, Elens L, Sprowl JA, et al. CYP3A4*22 genotype and systemic exposure affect paclitaxel-induced neurotoxicity. *Clin Cancer Res*. 2013;19(12):3316-3324. doi:10.1158/1078-0432.CCR-12-3786
12. Mielke S, Sparreboom A, Steinberg SM, et al. Association of paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. *Clin Cancer Res*. 2005;11(13):4843-4850. doi:10.1158/1078-0432.CCR-05-0298
13. Joerger M, von Pawel J, Kraff S, et al. Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2016;27(10):1895-1902. doi:10.1093/annonc/mdw290
14. Zhang J, Zhou F, Qi H, et al. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared with

body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. *Br J Clin Pharmacol*. 2019;85(10):2292-2301. doi:10.1111/bcp.13982

15. Hopkins JJ, Sawyer MB. A review of body composition and pharmacokinetics in oncology. *Expert Rev Clin Pharmacol*. 2017;10(9):947-956. doi:10.1080/17512433.2017.1347503
16. Shachar SS, Deal AM, Weinberg M, et al. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. *Clin Cancer Res*. 2017;23(3):658-665. doi:10.1158/078-0432.CCR-16-940
17. Ali R, Baracos VE, Sawyer MB, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Med*. 2016;5(4):607-616. doi:10.1002/cam4.621
18. Prado CM, Lima IS, Baracos VE, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol*. 2011;67(1):93-101. doi:10.1007/s00280-010-1288-y
19. Mir O, Coriat R, Blanchet B, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS ONE*. 2012;7(5):e37563. doi:10.1371/journal.pone.0037563
20. Massicotte MH, Borget I, Broutin S, et al. Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. *J Clin Endocrinol Metab*. 2013;98(6):2401-2408. doi:10.1210/jc.2013-1115
21. Wong AL, Seng KY, Ong EM, et al. Body fat composition impacts the hematologic toxicities and pharmacokinetics of doxorubicin in Asian breast cancer patients. *Breast Cancer Res Treat*. 2014;144(1):143-152. doi:10.1007/s10549-014-2843-8
22. van Doorn L, Crombag MBS, Rier HN, et al. The influence of body composition on the systemic exposure of paclitaxel in esophageal cancer patients. *Pharmaceuticals (Basel)*. 2021;14(1):47. doi:10.3390/ph14010047
23. Derstine BA, Holcombe SA, Ross BE, Wang NC, Su GL, Wang SC. Skeletal muscle cutoff values for sarcopenia diagnosis using T10 to L5 measurements in a healthy US population. *Sci Rep*. 2018;8(1):11369. doi:10.1038/s41598-018-29825-5
24. Krishnamurthy V, Zhang P, Ethiraj S, et al. Use of analytic morphomics of liver, spleen, and body composition to identify patients at risk for cirrhosis. *Clin Gastroenterol Hepatol*. 2015;13(2):360-368.e5. doi:10.1016/j.cgh.2014.07.042
25. Kraff S, Lindauer A, Joerger M, Salamone SJ, Jaehde U. Excel-based tool for pharmacokinetically guided dose adjustment of paclitaxel. *Ther Drug Monit*. 2015;37(6):725-732. doi:10.1097/ftd.0000000000000206
26. Joerger M, Huitema ADR, van den Bongard DHJG, Schellens JHM, Beijnen JH. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of paclitaxel in patients with solid tumors. *Clin Cancer Res*. 2006;12(7):2150-2157. doi:10.1158/1078-0432.CCR-05-2069
27. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33(2):261-304. doi:10.1177/0049124104268644
28. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res*. 2007;13(11):3264-3268. doi:10.1158/1078-0432.CCR-06-3067
29. Cespedes Feliciano EM, Lee VS, Prado CM, et al. Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study. *Cancer*. 2017;123(24):4868-4877. doi:10.1002/cncr.30950
30. Cespedes Feliciano EM, Chen WY, Lee V, et al. Body composition, adherence to anthracycline and taxane-based chemotherapy, and survival after nonmetastatic breast cancer. *JAMA Oncol*. 2020;6(2):264-270. doi:10.1001/jamaoncol.2019.4668
31. Chemama S, Bayar MA, Lanoy E, et al. Sarcopenia is associated with chemotherapy toxicity in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer. *Ann Surg Oncol*. 2016;23(12):3891-3898. doi:10.1245/s10434-016-5360-7
32. Trobec K, Kerec Kos M, von Haehling S, Springer J, Anker SD, Lainscak M. Pharmacokinetics of drugs in cachectic patients: a systematic review. *PLoS ONE*. 2013;8(11):e79603. doi:10.1371/journal.pone.0079603
33. Kumar GN, Walle UK, Bhalla KN, Walle T. Binding of taxol to human plasma, albumin and alpha 1-acid glycoprotein. *Res Commun Chem Pathol Pharmacol*. 1993;80(3):337-344.
34. Desmedt C, Fornili M, Clatot F, et al. Differential benefit of adjuvant docetaxel-based chemotherapy in patients with early breast cancer according to baseline body mass index. *J Clin Oncol*. 2020;38(25):2883-2891. doi:10.1200/JCO.19.01771
35. Beumer JH, Chu E, Allegra C, et al. Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology recommendations for 5-fluorouracil therapy. *Clin Pharmacol Ther*. 2019;105(3):598-613. doi:10.1002/cpt.124
36. Salgado TM, Quinn CS, Krumbach EK, et al. Reporting of paclitaxel-induced peripheral neuropathy symptoms to clinicians among women with breast cancer: a qualitative study. *Support Care Cancer*. 2020;28(9):4163-4172. doi:10.1007/s00520-019-5254-6
37. Bandos H, Melnikow J, Rivera DR, et al. Long-term peripheral neuropathy in breast cancer patients treated with adjuvant chemotherapy: NRG Oncology/NSABP B-30. *J Natl Cancer Inst*. 2018;110(2):djx162. doi:10.1093/jnci/djx162
38. Shimozuma K, Ohashi Y, Takeuchi A, et al. Taxane-induced peripheral neuropathy and health-related quality of life in postoperative breast cancer patients undergoing adjuvant chemotherapy: N-SAS BC 02, a randomized clinical trial. *Support Care Cancer*. 2012;20(12):3355-3364. doi:10.1007/s00520-012-1492-x
39. Hertz DL, Childs DS, Park SB, et al. Patient-centric decision framework for treatment alterations in patients with chemotherapy-induced peripheral neuropathy (CIPN). *Cancer Treat Rev*. 2021;99:102241. doi:10.1016/j.ctrv.2021.102241
40. Loibl S, Skacel T, Nekljudova V, et al. Evaluating the impact of relative total dose intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer—a pooled analysis. *BMC Cancer*. 2011;11(1):131. doi:10.1186/1471-2407-11-131
41. Derstine BA, Holcombe SA, Goulson RL, et al. Quantifying sarcopenia reference values using lumbar and thoracic muscle areas in a healthy population. *J Nutr Health Aging*. 2017;21(10):180-185. doi:10.1007/s12603-017-0983-3

SUPPORTING INFORMATION

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How to cite this article: Hertz DL, Chen L, Henry NL, et al. Muscle mass affects paclitaxel systemic exposure and may inform personalized paclitaxel dosing. *Br J Clin Pharmacol*. 2022;88(7):3222-3229. doi:10.1111/bcp.15244