PHARMACOTHERAPY

Comparison of Body Size, Morphomics, and Kidney Function as Covariates of High-Dose Methotrexate Clearance in Obese Adults with Primary Central Nervous System Lymphoma

Manjunath P. Pai[1]* Kenneth C. Debacker,[1] Brian Derstine,[2] June Sullivan,[2] Grace L. Su,[2,3] and Stewart C. Wang[2]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan; [2]Department of Surgery, Michigan Medicine, University of Michigan, Ann Arbor, Michigan; [3]Department of Medicine, VA Ann Arbor Health System, Ann Arbor, Michigan

Background High-dose methotrexate (HD-MTX) is used to treat primary central nervous system lymphoma (PCNSL), but potential differences in MTX clearance (CL) due to obesity have not been studied. We characterized the relationship between HD-MTX CL and computed tomography (CT)-generated body composition (morphomic), body size descriptors, and laboratory measurements in a cohort of obese and non-obese patients with PCNSL.

Methods Medical records from adult patients with PCNSL treated with HD-MTX over a 10-year period were queried. Individuals with CT data within 30 days of the first cycle of treatment were included. Population pharmacokinetic analysis was performed using a 2-compartment base structural model. We specifically compared body surface area (BSA) to standard body size, morphomic, and renal function estimation methods as covariates of HD-MTX CL.

Results The final data set consisted of non-obese (n=45) and obese (n=28) patients with 291 observations (3–7 samples per patient) with a mean (standard deviation) weight of 69.8 (11.6) kg and 104 (14.9) kg, respectively (p=0.0001). Vertebral body height was more informative than BSA of MTX CL. Similarly, a CL model incorporating age, albumin, and serum creatinine was more informative than kidney function equations and body size. The final model of MTX CL was based on age, albumin, serum creatinine, and vertebral body height.

Conclusions Common clinical variables coupled with vertebral body height are more predictive of first cycle MTX CL than BSA, alternate body size descriptors, and commonly used kidney function equations.

Key Words analytic morphomics, leucovorin, obesity, pharmacology, kidney function, body composition, pharmacokinetics.

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Primary central nervous system lymphoma (PCNSL) is a rare (4.4 cases per million persons annually) form of extranodal non-Hodgkin's lymphoma that is limited to the brain, leptomeninges, spinal cord, and eyes.[1] The median age at diagnosis is 65 years, and an increase in the incidence of this cancer has been noted over the past few decades.[2-5] The prevailing therapy

Conflicts of interest: S.C.W. and J.A.S. are inventors of the Analytic Morphomics: High Speed Medical Image Automated Analysis Method (US patent 14/014,485). All other authors have no conflicts of interest to disclose regarding this work.

*Address for correspondence: Manjunath P. Pai, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109; e-mail: amitpai@med.umich.edu.

for newly diagnosed PCNSL is methotrexate (MTX), primarily a competitive inhibitor of dihydrofolate reductase that is responsible for folate activation in the thymine and purine biosynthetic pathway.[6] Although MTX is a potent cytotoxic agent, poor blood-brain barrier permeability necessitates administration of high-dose methotrexate (HD-MTX), typically 1–8 g/m^2 in combination with whole-brain radiotherapy or other cytotoxic chemotherapy agents for treatment of PCNSL.[1] Administration of HD-MTX to target brain cancer cells can negatively impact normal cells resulting in significant toxicities. The major acute toxicities associated with HD-MTX include nephrotoxicity, neurotoxicity, mucositis, myelosuppression, and hepatotoxicity.[7] High plasma concentrations between 24 and 48 hours from dosing have been linked with an increased risk for these toxicities.[7] The elimination of MTX is primarily renal, and so hydration and urine alkalization are used to enhance MTX clearance (CL) and lower the risk of nephrotoxicity by reducing crystal formation in nephrons.[7] Therapeutic drug monitoring (TDM) of MTX is also performed to provide a pharmacokinetic (PK) guide for leucovorin rescue dosage.[8-10] Leucovorin or folinic acid is administered as an antidote to prevent death of normal cells by serving as the direct resource for the thymine and purine biosynthetic pathway. At present, there is no consensus on the optimal dose of HD-MTX or on the role of radiation in combination with MTX in the management of PCNSL.[1]

The rarity of PCNSL also limits our knowledge on the optimal dose of HD-MTX in special populations, such as obesity.[1] Although the association between obesity and PCNSL cancer survivorship is limited, data from breast, prostate, and colorectal cancer cohorts indicate poorer quality of life, a higher risk for cancer recurrence, and disease progression in obese patients.[11] To date, the literature on HD-MTX dosing in obesity is limited to a single case report in an obese (39.3 kg/m^2) patient treated with MTX 8–10 g/m^2 for osteosarcoma, leading to limited insights on potential differences in the PK of MTX across body size.[12,13] Selection of body surface area (BSA) as the metric for HD-MTX dosing is consistent with the traditional approach used with lowering the toxicity risk of most cytotoxic agents.[14,15] However the relevance of this dosing strategy has not been carefully evaluated in obese patients.[16] This is concerning given that more than a third of adult patients in the United States are obese.[17] Routine use of TDM in patients receiving HD-MTX provides an opportunity to rectify this limitation. Current models also demonstrate that the toxicity profile of HD-MTX is predicted by the area under the curve (AUC) after the first cycle of therapy. As a consequence, optimal prediction of CL is likely to aid empiric dosage selection. Reliance solely on BSA to define the dosage of HD-MTX in theory may not be as useful as incorporation of other readily available clinical variables predictive of MTX CL.

Potential empiric dosing strategies of HD-MTX, instead of g/m^2 dosing, may include use of alternate body size descriptors, body composition measurements, or estimated kidney function values predictive of MTX CL. Two major alternate body size descriptors include adjusted body weight (adjBW) and lean body weight (LBW) that are also mathematical transformations of height and body weight but, unlike BSA, account for differences by sex.[18] Patients with PCNSL undergo multiple radiologic assessments that can also be used to characterize individual body composition. Our group has developed analytical morphomic tools that use existing radiologic data to generate estimates of skeletal muscle, fat, and other relevant body phenotype measures that can serve as scalars of PK parameters.[19,20] Similar to body size, multiple equations exist to estimate kidney function that has traditionally included the Cockcroft-Gault formula for creatinine clearance (eCrCL) and more recently the Chronic Kidney Disease Epidemiology (CKD-EPI) equation for the glomerular filtration rate (eGFR).[21,22] The current investigation compared the PK of HD-MTX in obese and non-obese patients with PCNSL who had radiologic data for analytic morphomic assessment. Our objectives were to apply a semi-mechanistic approach to comparison of body size, morphomic, and kidney function estimating variables and functions as predictors of HD-MTX clearance in comparison to the current standard of BSA.

Methods

Ethics

This was a retrospective study conducted across the Michigan Medicine enterprise. Institutional review board approval was obtained from the University of Michigan prior to the collection of any patient data.

Design and Study Population

Data were retrospectively obtained from "DATADIRECT," a self-service clinical database developed and maintained by the University of Michigan. The query time frame was an approximately 10-year period between November 2007 and January 2018. Patient records were queried if the following criteria were satisfied: (i) patients greater than 18 years of age, (ii) diagnosis of PCNSL, (iii) therapy with intravenous MTX during the study period, (iv) measurement of MTX concentrations during the course of therapy, and (v) CT scan available within 30 days of the first measured MTX concentration. Data queried included patient demographics, encounters, MTX drug orders and administration times, and laboratory information. The clinical dataset was then matched to a radiologic database containing CT images to identify patients with data sufficient to generate analytic morphomic parameters. Data were password protected and stored on a secure platform maintained by the University. Data manipulation was accomplished using the R programming language and environment. Patients were excluded if they met any of the following criteria: (i) incomplete or missing MTX dosing information during the index course of therapy, (ii) lack of documentation of height and/or weight, (iii) CT imaging with an insufficient field of view to obtain morphomic measurements or image artifact impacting interpretation, and (iv) renal replacement therapy (including hemodialysis and continuous renal replacement therapy).

Analytic Morphomics

Individual morphomic parameters were computed as previously described.[23,24] In brief, a custom-built MATLAB-based (The Mathworks Inc., Natick, MA) algorithm was used to identify vertebral elements in a semiautomated manner from Digital Imaging and Communications in Medicine (DICOM) files of CT scans. These vertebral elements were then used to create an anatomic index. Consistent estimates of abdominal fat, skeletal muscle, and visceral cavity were obtained using measurements at the inferior aspects of the second (L2), third (L3), and fourth (L4) lumbar vertebral bodies. Volumetric estimates were made by multiplying measures of cross-sectional area by the height of the corresponding vertebral body (L2, L3, and L4). In the case of fat volume this included the summation of subcutaneous and visceral fat volumes. Descriptions of specific morphomic measures are accessible through the Morphomics Data Dictionary (available at http://www.med.umich.edu/surgery/morphomics/data_dictionary).

Alternate Body Size and Kidney Function Estimates

Alternative body size scalars including ideal body weight (IBW), adjBW, LBW, and BSA using Mosteller's adaptation were computed as previously described.18 In addition total body weight (TBW) scaled as a power function [(TBW/average TBW)$^{\beta}$] or as a fixed power function, allometrically as [(TBW/average TBW)$^{0.75}$] were also tested. Estimates of renal function were calculated using the Cockcroft-Gault and CKD-EPI (eGFR_CKD-EPI).[21,22] We also tested the four variable (age, sex, race, serum creatinine) and six variable (age, sex, race, serum creatinine, blood urea nitrogen, and albumin) Modification of Diet in Renal Disease (MDRD) formula referred to as MDRD4 and MDRD6, respectively.[25,26] The modified Cockcroft-Gault (mCG) equation was used with each of the scalars of body weight listed above ([(140 – age) × 0.85 if female/serum creatinine]), with weight removed so that independent effects could be tested.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic analyses were performed using Pkanalix2019R2 (noncompartmental analysis), Monolix2019R2, and Sycomore2019R2 (Monolix Suite2019R2, Antony, France: Lixoft SAS, 2019). For population PK analysis, the stochastic approximation expectation maximization (SAEM) algorithm was used within Monolix2019R2 and individual MTX dosing and concentration–time data. A two-compartment, first-order input, and linear clearance parameterized model structure was selected given repeated documentation of this model for the intravenous MTX concentration–time profile in the literature. Given that initial parameter estimates can influence final parameter estimates, we also applied the nonparametric adaptive grid (NPAG) using the PMetrics® library implemented through R for comparison with the literature.[27] We subsequently selected initial condition parameter estimates from a recent large study sample two-compartment model of HD-MTX.[28] As expected, our objective was to test a large

number of alternate body size (n=7), morphomic (n=36), kidney function estimate (n=4), and laboratory parameters (n=6) required testing and so this analysis was performed in a stepwise manner given the large number of potential permutations, described as follows. Alternate models included incorporation of covariates with discrimination between models based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). These model comparisons were performed using Sycomore2019R2 within the Monolix suite. Visual predictive checks and nonparametric distribution error (NPDE) checks were performed with each model run through an efficient pipeline process within Monolix2019R2.

Series 1

We tested the base model (no-covariates), which was followed up with each body size parameter that included TBW, allometrically scaled TBW ($[(TBW/80\ kg)^{0.75}]$), power-scaled TBW ($[(TBW/80\ kg)^{\beta}]$), IBW, adjBW, LBW. This was subsequently tested with each analytic morphomic parameter. Given the strong correlation between L2, L3, and L4 measurements subsequent analyses were limited to the L3 measurements expected for the volume measurements that integrated all three lumbar measurements.

Series 2

We tested each kidney function estimating equation with no other covariates and then with individual body size and morphomic parameters added in a stepwise manner as covariates of CL.

Series 3

We tested each laboratory parameter and demographic variable and identified the combination of age, albumin, and serum creatinine to be optimal (lowest AIC). Body size and morphomic parameters were then added in a stepwise manner as covariates of CL.

Given that the assay variability was not available to us, we relied on an additive and proportional error mode (COMBINED1 in Monolix) with initial conditions set to literature estimates. Patient demographics and morphomic measures were summarized using descriptive statistics stratified by the classification of obesity (body mass index [BMI] $\geq 30\ kg/m^2$). Between-group comparisons were accomplished using the Mann-Whitney U test and performed by sex for fair comparisons. Given that BSA serves as the dosing benchmark for MTX, the base model 1 was a two-compartment model with BSA as a covariate of CL. Since this base model (BSA only) was one of the least informative models, we selected BSA, age, albumin, and serum creatinine as covariates of CL to be the second referent model (base model 2). Statistical analyses were performed in Stata SE version 14.2 (Stata, StataCorp LLC, College Station, TX) at an α-level of 0.05.

Results

Study Population

A total of 104 adult patients with PCNSL treated with HD-MTX were identified. The median [min, max] age, height, and weight of the population was 66 [26, 86] years, 168 [152.4, 198.1] cm, and 80.7 [46.5, 180] kg, respectively. There were 50 (18 obese) males and 54 (21 obese) females in the sample. The mean [min, max] MTX dose was 13.25 [2.27, 20.5] g and 6.97 [1.11, 10.99] g/m^2. Computed tomography data for all analytic morphomic parameters tested were available for 73 patients (70% of the study population) and the demographics, key laboratory variables, and MTX dosing details are included in Table 1. Similar to the overall PCNSL group, approximately 38.4% of the patients met the classification of obesity. The obese and non-obese groups were comparable with exception of expected differences by group for weight, BMI, and BSA. Kidney function estimates based on eGFR were not different between the two groups. Similarly, no significant difference was observed with eCrCL between groups when weight was excluded but not when TBW was included (expected bias of this equation).

Observed Concentration Profile

A total of 291 concentrations were measured in the 73 patients included in the analyses with a median [min, max] of 4 [3, 7] samples per patient. Figure 1 illustrates the superimposable central tendency profiles of MTX concentrations in non-obese and obese patients. The mean (standard deviation (SD)) $AUC_{0\text{-}inf}$ was 2150 (2056) h•μM and 2582 (1625) h•μM in the non-obese and obese patients, respectively (p=0.349). The mean (SD) time to first and second

Table 1. Demographic Variables among Obese and Non-Obese Patients with Morphomic Data

Variable	Non-Obese (n=45) Mean (SD)	Obese (n=28) Mean (SD)	p-Value
Age (yrs)	64.1 (11.3)	64.9 (11.7)	0.793
Height (cm)	170 (8.9)	169 (10.7)	0.642
Total body weight (kg)	69.8 (11.6)	104 (14.9)	<0.001
BMI (kg/m^2)	24.0 (3.0)	36.5 (6.0)	<0.001
BSA (m^2)	1.81 (0.19)	2.20 (0.19)	<0.001
Serum creatinine (mg/dl)	0.80 (0.29)	0.82 (0.24)	0.774
BUN (mg/dl)	18.9 (8.1)	18.0 (9.8)	0.664
Albumin (mg/dl)	3.5 (0.4)	3.6 (0.4)	0.179
Hematocrit (%)	32.9 (4.3)	31.7 (5.1)	0.736
Methotrexate dose (g/m^2)	6.94 (1.91)	6.60 (1.89)	0.458
Methotrexate dose (g)	12.5 (3.70)	14.5 (4.46)	0.040
eCrCL_TBW (ml/min)	96.5 (44.5)	134 (56.5)	0.003
eCrCL_No weight (ml/min)	95.3 (34.1)	94.5 (37.6)	0.816
eGFR_CKD-EPI (ml/min/1.73 m^2)	86.5 (21.8)	87.7 (21.2)	0.735
eGFR_MDRD4 (ml/min/1.73 m^2)	97.7 (43.8)	89.5 (29.1)	0.379
eGFR_MDRD6 (ml/min/1.73 m^2)	93.9 (41.7)	89.3 (29.7)	0.619

BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; CKD-EPI = chronic kidney disease epidemiology equation; eCrCL = estimated creatinine clearance using Cockcroft-Gault equation with TBW or no weight; eGFR = estimate glomerular filtration rate; MDRD4 = four-variable Modification of Diet in Renal Disease equation; MDRD6 = six-variable Modification of Diet in Renal Disease equation; SD = standard deviation; TBW = total body weight.

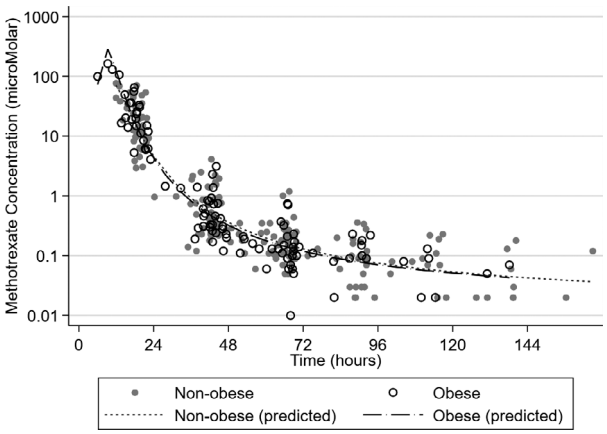

Figure 1. Observed (scatter) methotrexate concentrations and fractional polynomial fit (predicted) plot in non-obese and obese patients.

concentration measurements were 18.8 (4.8) hours and 42.0 (5.3) hours, respectively. The median [interquartile range (IQR)] concentration at this first concentration benchmark was 14.0 [7.98–34.7] μM and 19.6 [11.6–42.7] μM in the non-obese and obese groups, respectively (p=0.166). The median [IQR] concentration at this second concentration benchmark was 0.46 [0.29–0.95] μM and 0.46 [0.30–0.88] μM in the non-obese and obese groups, respectively (p=0.923). The proportion of patients above 10 μM was 64% in the non-obese and 79% in the obese group at first measurement. However, this difference was similar at the second measurement for concentrations above 0.5 μM, which was 46% in both the non-obese and obese groups.

Body Size and Analytic Morphomics

A summary of alternate body size descriptors and analytic morphomics is included in Table 2. Figure 2 provides an illustration of the CT scan cross plane translation into patient-specific regions of subcutaneous fat, visceral fat, and skeletal muscle area. Analytic morphomic data from L3 is presented as it is representative and comparable to those of L2 and L4, and these parameters are combined to provide estimates of fat, skeletal muscle, and total body volume by group. All body size and body composition parameters were significantly different in obese compared non-obese groups by sex with exception to IBW, vertebral body height, and fascia to front skin (in males).

Pharmacokinetic Analysis

The median parameter estimates through the NPAG analysis for CL, volume of the central compartment (V_1), intercompartmental clearance (Q), and volume of the peripheral compartment (V_2) were 8.30 L/hour, 47.6 L, 0.091 L/hour, and 3.47 L, respectively. These estimates closely matched the covariate unstructured model mean estimates of 10 L/hour, 51.8 L, 0.103 L/hour, and 4.5 L for CL, V_1, Q, and V_2, respectively, through SAEM. Table 3 provides a summary of the AIC values for the covariate unstructured model (None/None) along with the aforementioned series-based permutations. When comparing body size descriptors alone, use of IBW (height-based descriptor) had the lowest AIC and all other descriptors including BSA were less informative than a non-covariate structured model. Similarly, vertebral body height was the most informative analytic morphomic parameter. In relative terms, eCrCL using CG was more informative than eGFR equations but reliance on a CL model based on age, albumin, and serum

Table 2. Comparison of Body Size Descriptors and Analytic Morphomic Variables in Non-Obese and Obese Patients by Sex and Reported as the Mean (Standard Deviation)

	Female		Male	
Variables	Non-Obese (n=24)	Obese (n=15)	Non-Obese (n=21)	Obese (n=13)
Body weight descriptors				
Ideal body weight (kg)	56.1 (5.8)	55.3 (7.4)	72.4 (5.1)	71.2 (8.7)
Adjusted body weight (kg)	59.2 (6.0)	73.8 (9.1)[a]	74.1 (6.3)	85.4 (8.1)[a]
Lean body weight (kg)	40.5 (4.1)	51.7 (5.6)[a]	59.2 (5.7)	69.9 (6.4)[a]
Analytic morphomic-L3				
Vertebral body height (cm)	3.22 (0.32)	3.06 (0.37)	3.27 (0.31)	3.37 (0.27)
Vertebral body to front skin (cm)	10.2 (2.5)	15.0 (3.0)[a]	12.8 (3.30)	15.7 (3.08)[a]
Fascia to front skin (cm)	2.42 (0.93)	3.65 (0.93)[a]	2.19 (0.56)	2.29 (0.93)
Vertebral body to fascia (cm)	7.88 (2.30)	11.4 (2.92)[a]	10.5 (3.32)	13.3 (3.73)[a]
Spine to back skin (cm)	2.38 (1.13)	4.93 (1.67)[a]	2.12 (1.19)	3.97 (1.43)[a]
Body depth (cm)	21.9 (3.1)	29.1 (4.0)[a]	24.9 (3.40)	29.9 (3.43)[a]
Visceral cavity area (cm^2)	361 (68.3)	538 (125)[a]	523 (122)	673 (154)[a]
Subcutaneous area (cm^2)	202 (89.0)	416 (146)[a]	201 (76.6)	318 (85.4)[a]
Subcutaneous fat area (cm^2)	179 (91.0)	384 (136)[a]	173 (72.0)	284 (83.0)[a]
Visceral fat area (cm^2)	95.7 (62.7)	228 (96.5)[a]	173 (104)	303 (121)[a]
Skeletal muscle area (cm^2)	95.8 (14.2)	125 (24.9)[a]	141 (27.4)	167 (26.7)[a]
Total body area (cm^2)	563 (131)	955 (241)[a]	724 (175)	991 (165)[a]
Analytic morphomic-L2, L3, and L4 combined				
Fat volume (cm^3)	2502 (1312)	5468 (2047)[a]	3382 (1886)	5804 (1476)[a]
Skeletal muscle volume (cm^3)	862 (169)	1107 (247)[a]	1343 (335)	1599 (289)[a]
Total body volume (cm^3)	6741 (1872)	11511 (3355)[a]	10070 (3498)	14341(3072)[a]

[a] $p<0.05$, comparing obese to non-obese within sex.

creatinine (used to predict kidney function) resulted in the lowest reduction in AIC value. Vertebral body height further lowered this AIC value whereas all other body size and analytic morphomic variables increased the AIC. Table 4 includes a summary of two reference base models, where base model 1 represents current reliance on BSA to select doses, and base model 2 includes BSA, age, albumin, and serum creatinine. The final model incorporates vertebral body height and is associated with the lowest IIV for all four parameters. The following equation describes the final model for estimation of MTX CL:

$$CL = 6.87 - 0.508 \times \left(\frac{Age}{66}\right) + 0.642 \times \left(\frac{Alb}{4.0}\right) - (0.234 \times SCr) + 0.322 \times \left(\frac{VBH}{3}\right)$$

where, age is in years, Alb is albumin in g/dl, SCr is serum creatinine in mg/dl, VBH is vertebral body height in cm. Bootstrap analysis with 1000 bootstrap replicates to obtain 95% confidence intervals for all PK parameters is included in Table 4. Visual predictive check of the final model shows that the 50th percentile and variability fall within 90% confidence bounds (Figure 3). This good overall performance of the final model provides reasonable internal validation for concentrations collected less than 96 hours from dosing and less so for concentration beyond this time point. Given the sparse data at these later time-points, focus on evaluation of a two-compartment structure, and limited clinical relevance for this extended time period, further optimization was not performed. The overall predictive performance is also noted in Figure 4 through clear demonstration of symmetry in the individual weighted residual density and probability plots. Similarly, the NPDE analysis showed adequate predictability with a majority of values within a normal distribution between −2 and 2.

Discussion

Methotrexate has been in use as a cancer chemotherapy agent for the past seven decades. The similarity in the dose per unit surface area from mouse (0.018 kg), rat (0.25 kg), infant (8 kg), older child (20 kg), and adult (70 kg) compared to the dose per unit weight for methchlorethamine, MTX, 6-mercaptopurine, and actinomycin D serves as the basis for BSA-dosing of several cancer chemotherapy agents today.[15] However, unlike the stated generally accepted dose of 5 mg/day of MTX in adults treated in 1958, the dosage used today is 2000-fold higher (when considering PCNSL). In addition, upward shifts in the body weight

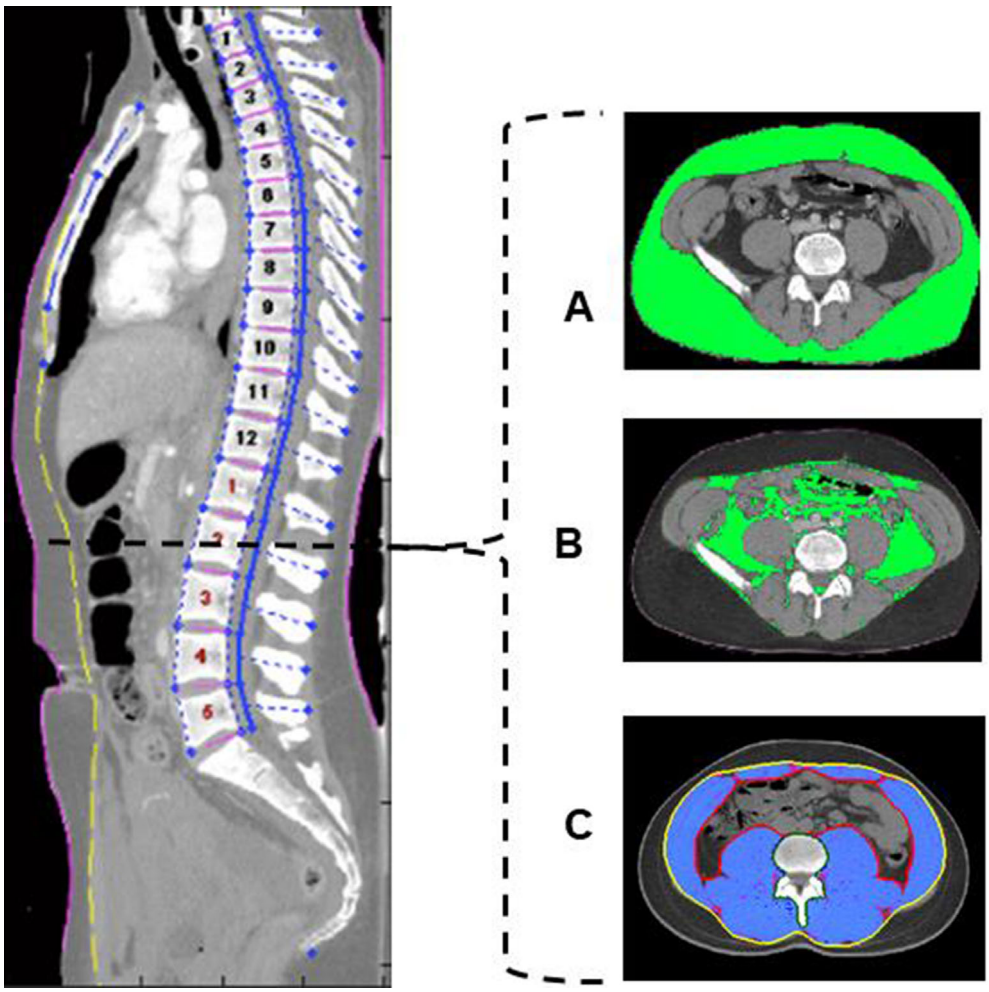

Figure 2. Illustrative example of patient-specific computed tomography imaging translation by analytic morphomics into subcutaneous fat area (A), visceral fat area (B), and skeletal muscle area (C).

distribution have changed the physique of patients treated with cancer over this time period.[16] Methotrexate is a small polar molecule with greater than 80% of this agent excreted unchanged in urine or through the bile (8.7–26%) with very limited metabolism.[29] Consistent with this physiochemical profile, distribution and clearance of this compound would not be expected to increase with adiposity and is not a component of current physiology-based PK models.[30] In contrast, models of kidney function presently based on eCrCL and eGFR may be better predictors of MTX CL. On the other hand, the key clinical eCrCL equation includes TBW that can bias the estimate of kidney function in obese patients. To date, a thorough examination of the independent effects of body size, composition, and kidney function on HD-MTX PK has not been performed in adults and the current literature on MTX dosing in obesity is limited to a single case report.[12,13,16] In contrast, a thorough examination of the relationship between BMI and HD-MTX CL has been evaluated in children and determined to not be a relevant covariate.[31] Clinicians have also used alternate dosing metrics in obese patients with cancer haphazardly, leading to issuance of guidance to curb this practice.[32] Given this knowledge gap, we sought to sort out body size, composition, and kidney function effects on HD-MTX plasma PK.

The richly sampled MTX concentration-time data used to inform leucovorin dose selection allowed us to evaluate the role of covariates on HD-MTX PK. The observed concentration-time data were almost superimposable in both groups stratified by the current definition of obesity. As clearly demonstrated by this thorough analysis, a base model without inclusion of BSA was better

Table 3. Summary of the Akaike Information Criterion for Each of the Tested Body Size and Morphomic Model Combinations without Kidney Function ("None"), with Kidney Function Equations, and Demographic/Laboratory Model Based on Age, Albumin (Alb), and Serum Creatinine (SCr)

Variables	None	CKD-EPI	MDRD4	MDRD6	CG	Age, Alb, SCr
None	188.46	182.80	186.19	182.51	180.30	162.90
Body weight descriptors						
Body surface area	192.25	178.52	190.74	194.85	187.77	170.16
Total body weight	195.61	180.24	191.20	186.00	182.72	169.80
Total body weight$^{\beta}$	189.16	181.65	190.97	193.57	181.34	170.69
Total body weight$^{0.y}$	194.58	181.44	186.83	187.78	182.81	167.12
Ideal body weight	187.30	184.57	191.23	185.50	182.65	166.01
Adjusted body weight	189.80	185.08	189.65	188.66	182.22	166.46
Lean body weight	190.58	182.09	194.09	186.95	182.03	170.45
Analytic morphomic—L3						
Vertebral body height	185.74	179.46	187.04	186.59	175.00	162.31
Vertebral body to front skin	190.24	182.14	191.66	189.28	184.57	166.68
Fascia to front skin	190.92	179.21	190.72	191.22	179.34	166.10
Vertebral body to fascia	190.63	182.60	186.78	187.59	180.51	169.31
Spine to back skin	192.57	180.65	189.17	185.51	182.92	163.89
Body depth	189.07	179.31	188.28	182.85	179.32	165.57
Visceral cavity area	196.09	181.61	188.40	184.27	180.04	169.96
Subcutaneous area	189.59	184.51	190.43	185.79	181.92	163.56
Subcutaneous fat area	193.04	184.46	189.54	185.13	182.66	164.08
Visceral fat area	188.15	183.87	188.68	188.58	181.17	169.39
Skeletal muscle area	187.76	182.70	189.86	184.69	184.45	166.86
Total body area	193.97	177.35	190.47	185.23	183.31	165.36
Analytic morphomic—L2, L3, and L4 combined						
Fat volume	196.50	182.70	185.77	189.16	184.04	165.92
Skeletal muscle volume	187.83	184.31	189.29	189.11	179.28	167.72
Total body volume	189.21	180.11	186.62	185.12	184.54	166.86

CG = Cockcroft-Gault equation without weight; CKD-EPI = Chronic Kidney Disease Epidemiology equation; MDRD4 = four-variable Modification of Diet in Renal Disease equation; MDRD6 = six-variable Modification of Diet in Renal Disease equation.

Table 4. Parameter estimates of the two reference base models, final model, and bootstrap analysis

Parameter	Base Model 1	Base Model 2	Final Model	Bootstrap of Final Model	
				Estimate	95% CI
AIC	192.25	170.16	162.31		
CL (L/hr)	8.67	11.1	6.87	7.58	3.16–14.31
V_1 (L/hr)	50.4	45.6	42.4	46.22	39.10–53.75
Q (L/hr)	0.097	0.092	0.0825	0.0919	0.0693–0.117
V_2 (L/hr)	4.10	3.25	2.88	3.54	2.47–4.76
Covariate effect on CL					
BSA	0.126	−0.094			
Albumin		0.689	0.642	0.662	0.280–1.057
Serum creatinine		−0.234	−0.234	−0.244	−0.416 to −0.092
Age		−0.539	−0.508	−0.524	−0.795 to −0.271
Vertebral body height			0.322	0.393	0.0238–0.773
IIV (%)					
CL	21	16	16	16	12–19
V_1	12	14	11	9.6	5.1–16
Q	54	49	48	54	39–67
V_2	54	59	55	55	42–67
Residual variability					
Additive	0.0012	0.0023	0.0013	0.0020	0.000095–0.0060
Proportional	0.25	0.24	0.24	0.22	0.18–0.26

AIC = Akaike information criterion; BSA = body surface area; CI = confidence interval; CL = clearance; IIV = interindividual variability; Q = intercompartmental clearance; V_1 = volume of the central compartment; V_2 = volume of the peripheral compartment.

than inclusion of BSA. Methotrexate CL was best related to age, serum creatinine, and albumin, variables that are key components of eGFR and eCrCL estimation. In relative terms, body size and composition were less influential on the model of MTX CL. Although the final model

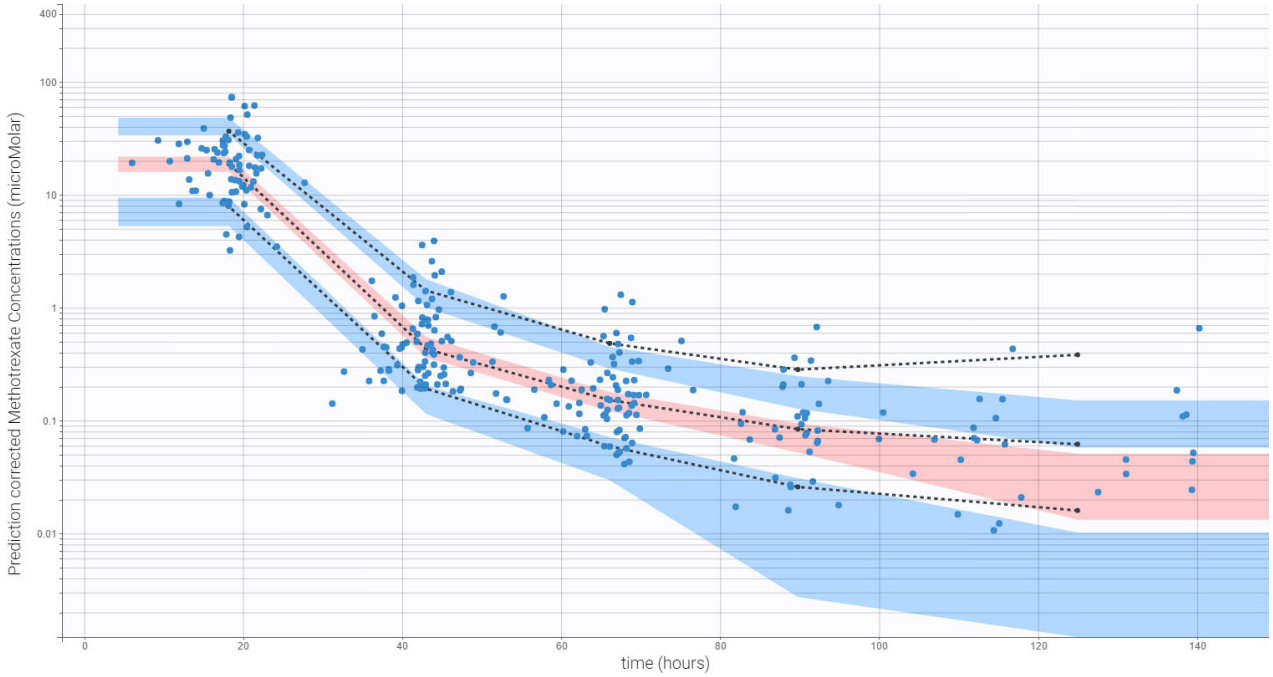

Figure 3. Prediction corrected visual predictive check plot of the final model on a $\log_{10}$ scale showing the observed data (scatter data) against the 10th, 50th, and 90th percentile line plots of the observed data against the 90% confidence intervals (pink and blue shade smoothed by linear interpolation) for the model-simulated data.

included vertebral body height, this parameter may simply represent improved empiric kidney function estimation for this agent.[33]

Vertebral body height has previously been shown to be correlated with kidney length.[34-36] Batson and Keats evaluated kidney size from 200 patients (56% male), 15–77 years of age, 75% between 20 to 60 years of age. Interestingly, 97.3% of the 400 measurements were within the range of L1 to L4 measurements and were independent of age and sex.[32] Kidney size correlates with kidney function but there are no published nomograms to provide comparative data to benchmark kidney size in this manner.[36] Our finding of this correlation between CL and vertebral body height suggests that characterization of kidney size could be an informative parameter. Although kidney size was not directly measured through analytic morphomics in this instance, such an evaluation is plausible with this technology in the future. These findings are in line with several population PK studies that document the close relationship between HD-MTX CL and kidney function.[28,37-40]

A population PK study in children and adults treated with HD-MTX for PCNSL revealed typical values of V_1, CL, Q, and V_2 were 24.5 L, 6.67 L/hour, 0.047 L/hour, and 1.32 L, respectively; much lower than the values observed in our study.[37] These values match several studies that have been performed in Asian patients with smaller body habitus.[40-42] In contrast, a study in European patients reported base model estimates for V_1, CL, Q, and V_2 as 34.0 L, 10.8 L/hour, 0.35 L/hour, and 6.3 L, respectively, which more closely match estimates from the present study.[38] In their model only CrCL and BSA served as covariates of CL and no other body size or laboratory values were predictive of other PK parameters.[38] Similarly in the most comprehensive population PK model to date, base model estimates for V_1, CL, Q, and V_2 as 52.1 L, 12 L/hour, 0.13 L/hour, and 5.6 L, respectively, where CL was parameterized as a function of eGFR and allometrically scaled to TBW.[28] In the present study, we show that allometrically scaling TBW is not more informative than other body size descriptors. Also, none of these prior studies have evaluated the potential influence of morphomic and alternate body size descriptors as covariates of MTX PK that were also not informative overall.

The influence of body composition on the pharmacokinetics of cancer chemotherapy has recently been reviewed.[16] This analysis reveals that cross-sectional imaging, as used in the current study, provides reliable estimates of body composition in oncology patients. However, the vast majority of studies to date have focused on the association between body composition and

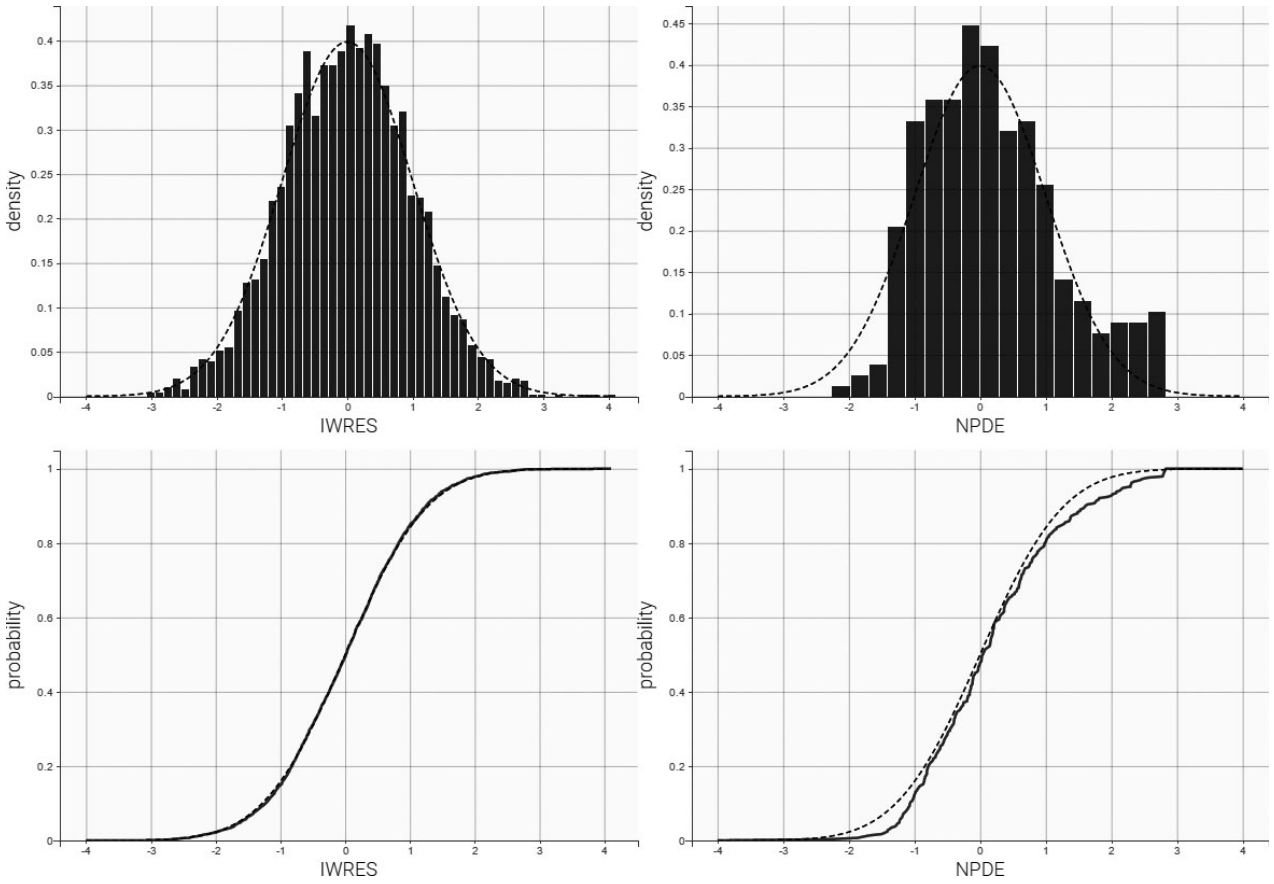

Figure 4. Goodness of fit plots of the final model represented by the density and probability plots of the conditional distribution of the individual weighted residuals (IWRES) and the nonparametric distributional error (NPDE).

the risk of chemotherapy toxicity.[16] In these studies, patients with lower lean mass (computed based on muscle area) have higher observed drug concentrations and experience a higher incidence of adverse events. These differences have been presumed to be a result of altered volume of distribution and CL. In the present study, we included individuals with a median [min, max] skeletal muscle area at L3 of 123 [66.5, 212] cm^2 that match the range observed in a previous study used to estimate lean mass.[43] However, we were not able to demonstrate a meaningful relationship between these body composition metrics and MTX PK parameters. Our findings are consistent with recent evaluation of skeletal muscle and 5-fluorouracil PK in patients with colorectal cancer.[44] No differences in fluorouracil AUC were observed in patients with low skeletal muscle area compared to patients with normal skeletal muscle for age.

Our study has limitations inherent to its retrospective design. Exclusion of patients without CT data was unlikely to have influenced our findings given that the exposure profiles among obese and non-obese patients were almost superimposable. Our analyses were also limited to the first cycle of therapy; previous studies have demonstrated changes in PK of MTX between cycles.[37-42] We chose to limit our analysis to the first cycle to reduce the potential influence of MTX use itself on body composition and CL that could cloud our interpretation of these relationships. Furthermore, these metrics are likely to be less relevant once TDM is performed after the first cycle given that individual PK parameter estimates can inform dose management in subsequent cycles.[38] We also did not evaluate time-varying models of MTX CL due to alterations in kidney function or incorporate the influence of urinary alkalization as this information was missing. Despite these limitations, our study is the first to disambiguate the relationship between HD-MTX PK, body size, composition, and kidney function in adult patients with PCNSL. Demonstration that obesity has limited influence on MTX PK implies that altered dosing schemas are unlikely in this population. Dosing

MTX based on BSA is simple but expected to be less precise than factoring age, albumin, and serum creatinine for this agent.

Conclusion

The plasma PK of HD-MTX are comparable in obese and non-obese adult patients with PCNSL. Body size does not account for interindividual variability in HD-MTX PK, whereas variables associated with kidney function estimation and vertebral body height are predictive of clearance.

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Contributions

M.P.P. and S.C.W. conceived of the study; B.D. constructed the queries, extracted morphomics data from the database, and reviewed morphomic measurements for accuracy; M.P.P. and K.C.D. performed the pharmacokinetic and statistical analyses; all authors contributed to the design, writing, and editing of the final manuscript for submission.

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