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ORIGINAL ARTICLE

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Population pharmacokinetic and limited sampling models for carboplatin administered in high-dose combination regimens with peripheral blood stem cell support

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Abstract *Objective:* By means of a nonlinear mixed effect modeling technique, a population pharmacokinetic (PK) model was developed to evaluate the effects of a variety of covariates on clearance and other pharmacokinetic parameters of ultrafilterable carboplatin administered in high-dose combination regimens with peripheral blood stem cell support. In addition, single-sample and two-sample limited sampling models (LSMs) were derived to estimate carboplatin's AUC that could be used in the design of drug dosing regimens. *Methods:* A total of 44 female patients with advanced ovarian cancer participated in two phase I studies. All 44 patients received a high-dose carboplatin chemotherapy with other anticancer drugs. A population PK model was applied to the plasma concentration-time data of ultrafilterable carboplatin using the NONMEM and Xpose computer programs. The Xpose program utilized a general additive modeling technique to identify significant patient covariates and PK parameter relationships. The resultant PK model was validated using a bootstrap method. Stepwise linear regression analyses were used to develop LSMs based on the correlation between carboplatin's AUC and plasma concentrations. *Results:* The best structural covariate-free model for high-dose carboplatin was a linear two-compartment model with an exponential error model to account for intersubject variability and a CCV error model to account for intrasubject variability. Subsequently, a final covariate model for clearance (l/min) was obtained as follows: $TVCL = 0.101 + 0011*(WT-62.35)-0.0658*(SCR-0.65)$ where WT is body weight (kg) and SCR is serum creatinine (mg/dl). Both WT and SCR were found to significantly influence carboplatin's total clearance. It was determined that the best single-sample LSM was $AUC_{LSM} = 0.553*C_{240min}$ ($r = 0.998$). *Conclusion:* Both a population PK model and a LSM for high-dose carboplatin were developed following its administration in combination chemotherapeutic regimens with peripheral blood stem cell support. In both cases, the models performed well when analyzed in the context of the retrospective and bootstrap analyses. Prospective studies in ovarian cancer patients should be conducted to further tailor the current models.

Keywords Limited sampling model · Population pharmacokinetic model · High-dose carboplatin

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Introduction

Carboplatin, a second-generation platinum compound, has appreciable activity against a broad spectrum of malignancies. It has qualitatively similar antitumor activity and is structurally related to cisplatin, but differs by having a bidentate dicarboxylate chelate ligand replacing the two chlorine atoms [17]. It is considered a cell cycle phase-nonspecific agent, which reacts with nucleophilic sites on DNA, causing intrastrand, interstrand, and DNA-protein crosslinks. In humans, it has wide antitumor activity with proven efficacy in ovarian cancer, germ cell tumors, non-small-cell and small-cell lung cancer, head and neck cancer, soft-tissue sarcoma, urinary tract tumors, breast cancer and brain tumors [3].

The majority of pharmacokinetic studies of carboplatin have utilized single doses in the range 20–500 mg/m^2

[8, 18, 24]. There is reasonable consistency in the total clearance, renal clearance, and volume of distribution values for both total platinum and ultrafilterable platinum. These studies have demonstrated that carboplatin undergoes dose-independent pharmacokinetics yielding dose-proportional increases in peak plasma concentration and area under the concentration-time curve (AUC) values [12]. Several studies in adults have shown that the AUC of plasma ultrafilterable carboplatin has a major impact on its toxicity and probably its activity [14].

Carboplatin is not appreciably metabolized but is hydrolyzed to aquated and hydroxylated compounds. Renal clearance is the main route of excretion, with about 50–75% of the total platinum administered as carboplatin excreted in the urine in 24 h [8, 18, 24]. There is a strong correlation between carboplatin's total clearance and its renal clearance. Several methods have been proposed to adjust the dose of carboplatin according to renal function, the main source of interindividual variability of carboplatin elimination. In these methods, the prediction of an individual carboplatin clearance is based on the radioisotopic determination of the glomerular filtration rate (GFR), the measurement of creatinine clearance [4], or calculation from standard covariates [i.e. serum creatinine (SCR), weight (WT), age, and sex] [5].

Myelosuppression, especially thrombocytopenia, is the dose-limiting toxicity of carboplatin. Plasma concentrations and the AUC of non-protein-bound carboplatin have been found to correlate well with the degree of thrombocytopenia [8, 10, 18, 24]. The paucity of non-hematogenous dose-limiting toxicities at conventional doses makes carboplatin an excellent drug for dose escalation with growth factor and bone marrow support. This approach has been reported in ovarian, lung, breast, testicular, and brain cancer [8, 18, 24].

There are limited pharmacokinetic data available for high-dose carboplatin regimens. Studies previously completed by us indicate that the pharmacokinetic parameters of high-dose carboplatin agree with those obtained at lower doses, suggesting that dose-independent pharmacokinetic properties are preserved at high doses. It has also been shown that Calvert formula-based dosing to obtain desired high AUC values is a reasonable approach [20, 21]. The current investigation extended our previous noncompartmental analyses of high-dose carboplatin pharmacokinetics by the use of population-based and limited sampling models (LSMs). Population pharmacokinetic models account for intrasubject variability by identification of covariates or patient variables that influence the pharmacokinetics of the drug. It is through such covariate-pharmacokinetic parameter relationships that individual and optimal drug doses can be selected. The LSM was derived from the population model to allow carboplatin AUC values to be predicted from a small number of plasma samples.

Methods

Patient population

A total of 44 female patients with advanced ovarian cancer participated in two phase I studies conducted at Fox Chase Cancer Center (FCCC). Of these 44 patients, 24 participated in the phase I study of high-dose chemotherapy [20] with autologous peripheral blood stem cells induced by chemotherapy and GM-CSF, which was conducted in 1991 and 1992 at FCCC, and the remainder participated in a phase I study of high-dose carboplatin, paclitaxel and topotecan with autologous peripheral blood stem cell support conducted between 1996 and 1997 [21].

The inclusion criteria for participation in these studies were considered standard for phase I trials, and have been presented previously [20, 21]. Patient demographics and baseline laboratory values are given in Table 1.

Study design and assay method

Patients with advanced ovarian cancer were entered into a two-cycle chemotherapy treatment regimen. Patients were permitted to enter the next treatment cycle after a minimum 4-week drug-free washout period. Paclitaxel and carboplatin were administered in the first investigation [20], whereas topotecan was included in the second study chemotherapy [21]. Chemotherapy was administered on an inpatient basis. On day 1 of the first cycle, 250 mg/m^2 of paclitaxel was administered as a 24-h continuous intravenous infusion immediately followed by carboplatin as a 2-h intravenous infusion in 500 ml dextrose solution. In the second trial, a 24-h continuous infusion of either 10 or 12.5 mg/m^2 of topotecan was commenced at the completion of the carboplatin infusion.

All carboplatin doses were based on the Calvert formula [4] [actual dose = AUC(GFR + 25); dose mg, AUC mg·min/ml, GFR ml/min]. In the first trial [20], carboplatin doses were calculated to achieve a target AUC of 12, 16 or 20 mg·min/ml using the Cockcroft-Gault equation [7] to estimate the GFR. Carboplatin doses were designed to achieve AUC values of 16 mg·min/ml in the second trial [21] with GFR calculated according to the Jelliffe equation [13].

All blood samples for the measurement of carboplatin plasma concentrations were obtained during the first cycle. Blood samples (5 ml each) for carboplatin measurements were designated to be collected at the end of infusion, and at 0.083, 0.25, 0.5, 1, 2, 6, 12, 18, and 24 h after infusion. Plasma was separated by centrifugation and an aliquot of plasma was immediately ultrafiltered (molecular weight cutoff 30 kDa; Millipore Corporation, Bedford, Mass.) to yield an ultrafiltrate sample. Ultrafiltrate samples were stored frozen at –70°C until analyzed for platinum. The ultrafiltrate samples were diluted in duplicate with 0.2% nitric acid containing 0.1% (v/v) Triton X-100 and

Table 1. Summary of covariates from ovarian cancer patients who received high-dose carboplatin

Covariate	Symbol	Median	Range
Age (years)	AGE	49	23–62
Body surface area (m^2)	BSA	1.67	1.36–2.4
Height (cm)	HT	168.5	152.4–190
Weight (kg)	WT	62.35	41–15
Albumin (g/dl)	ALB	3.65	1.8–4.3
Serum creatinine (mg/dl)	SCR	0.65	0.2–1.2
Total bilirubin (mg/dl)	TBIL	0.5	0.1–1
Lactate dehydrogenase (U/l)	LDH	423	107–980
SGOT (U/l)	OT	19.0	4.0–187.0
SGPT (U/l)	PT	25	9–279

injected (20 μl) onto a flameless atomic absorption spectrophotometer (model 3100; Perkin-Elmer, Norwalk. Ct.) [20]. Platinum contents were determined in individual ultrafiltrate samples and then converted into the ultrafiltrate or unbound carboplatin concentrations.

Development of the population pharmacokinetics model

The goal of model development was to derive a population pharmacokinetic model of carboplatin based on plasma ultrafiltrate carboplatin concentrations that coupled with the inclusion of patient-specific covariates would adequately characterize the individual carboplatin concentration-time profiles. The development of the population pharmacokinetic model for carboplatin followed three distinct steps with a fourth step used for model validation [11, 16].

The pharmacokinetic analyses were performed by means of nonlinear mixed-effect modeling using the computer program NONMEM, version V, with double precision [1]. The first-order (FO) estimation method was used to obtain initial parameter estimates that were used as input in the FO conditional estimation (FOCE) method which generated the final pharmacokinetic parameters. Covariate selection was completed by general additive modeling (GAM) with the Xpose program. version 2.0 [15] running within the S-plus 2000 statistical package (MathSoft Corporation, Seattle, Wash.). Diagnostic graphs and additional statistical analyses were performed with JMP software, version 3.2.2 (SAS Institute, Cary, N.C.) and S-plus 2000.

Step 1: covariate-free population pharmacokinetics model

The goal of this step was to select the best structural pharmacokinetic model coupled with the proper statistical model without inclusion of covariates. Based on an initial examination of the carboplatin concentration-time curves, potential pharmacokinetic models considered were linear one- and two-compartment models. Statistical intrasubject variability models considered both the constant coefficient of variation and additive error models, whereas exponential and additive error models were considered for intersubject variability. For all statistical models, errors were assumed to be normally distributed with an expected population mean of zero. The structure of the covariance matrix was diagonal with the assumption that intersubject variability (i.e. ETAs) were uncorrelated. Evaluations of several different error models were based on values for individual prediction (IPRED), individual residual (IRES), and a value (IWRES) proportional to the ''individual weighted residual''. These values were based on the difference between the population mean and the individual intersubject variability measured by the NONMEM variable, ETA. The best model was selected from the criteria of the NONMEM minimum objective function value (–2 times the log likelihood function, LLF), and diagnostic plots. The test statistic was equal to $LLF_{reduced}-LLF_{full}$ (the difference between the full model LLF and the reduced model LLF). This statistic is an approximate chi-squared distribution with q degrees of freedom, where q is the number of parameters whose values are fixed in the reduced model. Here the significance level was 0.05.

Step 2: development of covariate population pharmacokinetic model

GAM was utilized to determine which covariates (listed in Table 1) were significantly related to each pharmacokinetic parameter and whether this relationship was linear or nonlinear. In addition to the covariates in Table 1, the following indicator variables were added to the GAM analysis:

$$X1 = \begin{cases} 1 & \text{for study 1} \\ 0 & \text{for study 2} \end{cases}$$

$$X2 = \begin{cases} 1 & \text{when Taxol and Topotecan were used before carboplatin} \\ 0 & \text{when Taxol was used before carboplatin} \end{cases}$$

The individual Bayesian estimate for each pharmacokinetic parameter generated in step 1 for the best structural model and the individual covariates were used as input for the GAM analysis. The covariates were centered at the median value for each covariate. At each step in the GAM analysis, forward stepwise regression was used in conjunction with the Akaike's information criterion (AIC) to determine if individual covariates should be added, deleted or replaced in the final regression model. Visual examination of plots of intersubject variability (ETA) obtained for each pharmacokinetic parameter from step 1 versus each covariate was also used to help identify whether a covariate might be significantly related to the pharmacokinetic parameter and the nature of that relationship.

Case deletion diagnostics (i.e. studentized residuals and Cooks distances) were performed in conjunction with GAM analysis to identify potential outliers, individuals that could have a disproportionate effect on the covariate-pharmacokinetic relationship [15].

Step 3: development of the covariate population pharmacokinetic model

Each candidate covariate identified in the final GAM model (step 2) was further evaluated in the covariate-free population pharmacokinetic model derived in step 1. All continuous covariates were centered on their median values. A backward deletion strategy was used to determine which candidate covariates entered the final population model [16]. A covariate was retained in the model if the NONMEM objective function increased at least 10.83 ($P < 0.001$) upon its removal from the model, otherwise the covariate was deleted from the model. This conservative approach ensured that only the most meaningful covariates entered the model.

The population pharmacokinetic model derived in this step was evaluated by various measures of predictive performance [2, 11]. For each pharmacokinetic parameter, the percentage prediction error (PE_j) was calculated as:

$$PE_j = \frac{TVPK_j - PK_j}{TVPK_j} * 100$$

where $TVPK_j$ is the typical value for the pharmacokinetic parameter for patient j, and PK_j is the true or individual Bayesian estimated pharmacokinetic parameter for patient j.

Step 4: validation of the final population pharmacokinetic model

A bootstrap approach was used to validate the population pharmacokinetic model [9]. The bootstrap method was applied independently to both the covariate selection and the final population pharmacokinetic parameter selection processes.

First, 100 bootstrap datasets were generated with resampling from the original patient dataset. The best structural model was estimated for each bootstrap dataset as developed in step 1 for the original dataset. A GAM analysis (step 2) was completed with each set of pharmacokinetic parameters obtained in step 1 and the covariates for each bootstrap dataset. Once the GAM analyses were completed for each bootstrap dataset, the distributions of the candidate covariates were compared to the set of candidate covariates obtained from the original dataset.

In the second bootstrap validation exercise, the final population pharmacokinetic model, originally obtained in step 3, was applied independently to an additional 100 datasets. The reestimated pharmacokinetic parameters, and their variability were compared to the final set of parameters obtained from the original patient dataset.

Development of a LSM for estimating the AUC of carboplatin

The final population model for carboplatin was used as a basis to derive a LSM that correlated ultrafiltrate carboplatin concentrations to AUC. Since uniform blood sampling times are necessary to specify the set of ultrafiltrate carboplatin concentrations, the population model was used to simulate the set of carboplatin concentrations for the 44 patients used to develop the LSM. The population model also produced the AUC values (dependent variable) for the 44 patients used in the step-wise linear regression procedure along with the ultrafiltrate carboplatin concentrations (independent variables). All combinations of one and two carboplatin concentrations were evaluated. The regression equations that yielded the highest correlation coefficient corresponded to the best one- and two-point concentration estimators of the AUC.

The resultant regression equation parameter (i.e. estimate of slope and standard error of this estimate) was compared to the analogous parameters obtained from the LSM using the complete 44-patient dataset.

Comparison of population model, LSM and Calvert formula dosing approaches

Two AUC values were derived from the population approach. One, AUC_{Bay} was determined from the population model using Bayesian post-hoc estimation and the patient's individual carboplatin concentration-time data. The other, AUC_{TVCL}, was obtained from the final population model for the TVCL. The AUC predicted from the one-point LSM model was indicated as AUC_{LSM}, whereas the AUC targeted in the dosing design stage was indicated as $AUC_{Calvert}$. The AUC computed by the individual concentration-time curve fitting was indicated as AUC_{Actual}.

Results

Step 1: covariate-free model

The best structural covariate-free model for high-dose carboplatin was a linear two-compartment model with an exponential error model to account for intersubject variability and a CCV error model to account for intrasubject variability. The criteria used to select this model included the NONMEM objective function and visual examination of IWRES and IPRED values. It was found that the best two-compartment model yielded IWRES values that were randomly distributed around zero between –0.5 and 0.5.

Step 2: GAM analysis

GAM analysis identified a set of candidate covariates (see Table 2) that were further evaluated in step 3 in the development of the population model. All candidate covariates were linearly related to the corresponding pharmacokinetic parameter except the nonlinear relationship found between CL and WT. The nature of the nonlinear relationship between CL and WT was approximately sigmoidal in shape with CL values reaching a plateau as WT increased. To simplify the modeling algorithm, a linear relationship between CL and WT was implemented in the covariate model. The highly significant correlation between SCR and CL was anticipated based on the primary pathway of renal excretion for carboplatin. None of the patients was diagnosed as an outlier in the GAM analysis based on the studentized residuals and Cooks distance tests.

Table 2. Patient covariates identified in the GAM procedure

Parameter	Candidate covariates for each parameter
CL	WT, SCR
V1	TBIL, WT
Q	ALB
V2	ALB, SCR, AGE

Step 3: final population pharmacokinetic model

A final population pharmacokinetic model was obtained by combining the covariate-free model (step 1) and the candidate covariates (step 2) into a backward deletion technique within a NONMEM parameter estimation scheme. The final population model is as follows:

$$TVCL[\mathrm{L/min}] = 0.101 + 0011 * (WT - 62.35) - 0.0658 * (SCR - 0.65)$$

$$TV_1[\mathrm{L}] = 15.5 + 0.163 * (WT - 62.35)$$

$$TVQ[\mathrm{L/min}] = 0.0132 - 0.0103 * (\mathrm{ALB} - 3.65)$$

$$TV_2[\mathrm{L}] = 7.07 - 3.61 * (\mathrm{ALB} - 3.65)$$

where TVPK is the typical value for each pharmacokinetic parameter [CL, V_1, Q, V_2]. The agreement between observed and model-predicted ultrafiltrate carboplatin plasma concentrations (*PRED*) is illustrated in Fig. 1. There are neither substantial nor systematic deviations from the line of identity indicative that the model characterizes the overall behavior of the data. Examination of the residuals indicates that the assumption of random effects was appropriate since the residuals were evenly distributed around zero.

Table 3 lists the percentages of the prediction errors for both the final covariate and covariate-free population models. The inclusion of covariates reduced the mean prediction error and standard deviation of the prediction error for each pharmacokinetic parameter. An assessment of how well the typical value of clearance predicted each patient's true or Bayesian estimated

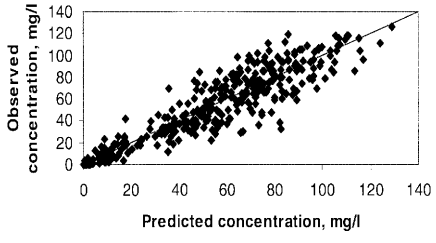

Fig. 1. Observed versus final population model-predicted carboplatin ultrafiltrate plasma concentrations

Table 3. Prediction error (PE_j) for covariate-free and final covariate population pharmacokinetic models for high-dose carboplatin

Parameter	PEj for covariate-free model		PEj for final covariate model	
	Mean	SD	Mean	SD
CL (l/min.)	–9.97	27.56	–5.18	22.62
V1 (l)	3.20	16.57	1.88	11.10
Q (l/min.)	7.13	32.56	–0.11	22.56
V2 (l)	–12.75	61.75	1.19	36.40

clearance can be seen in Fig. 2. There is a moderate degree of agreement between these two estimates of clearance ($r = 0.51$).

Validation of population pharmacokinetic model

The first bootstrap validation procedure repeated steps 1 and 2 for each of the 100 bootstrap datasets to assess the candidate covariate distribution via GAM. Table 4 provides the frequency or percentage of times each covariate entered the best GAM model for each pharmacokinetic parameter. For all the pharmacokinetic parameters, the candidate covariates identified by the original GAM entered the bootstrap because the frequencies of these candidates in bootstrap were greater than 50%. Therefore, the results derived from the bootstrap data supported the results from the original GAM analysis conducted with the actual patient data.

The population model developed in step 3 from the original dataset was refitted to each of the 100 bootstrap datasets using NONMEM. A comparison of the pharmacokinetic parameters estimated from the original dataset and the bootstrap datasets indicate a close agreement in the mean parameter values with differences of less than 5% (see Table 5). The magnitude of variability of the estimated parameters from the bootstrap datasets was generally low with coefficients of variation less that 15%, except for V_2 in which the coefficient of variation was 44%.

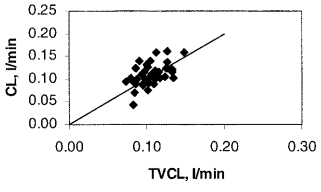

Fig. 2. Individual patient population model clearance (TVCL) values versus each patient's true clearance (CL) values. Regression line: $y = 0.0339 + 0.710x$ ($r = 0.515$)

LSM for AUC for high-dose carboplatin

The final population pharmacokinetic model was used to simulate carboplatin concentrations at distinct times coinciding with those stated in the original protocol. These simulated concentrations and the associated AUCs were used in the regression analyses to obtain both a one-point and a two-point LSM. Simple linear regression analysis found the carboplatin concentration measured at 240 min (2 h after the end of the 2-h infusion) was best correlated with AUC (mg·min/ml) and yielded the following LSM:

$$AUC_{LSM} = 0.553 * C_{240\,\mathrm{min}}, \quad r = 0.998$$

where $C_{240\mathrm{min}}$ (mg/l) is the carboplatin concentration at 240 min from the start of the infusion. The standard error of the slope was 0.0058 (Fig. 3).

The multiple regression analysis of the carboplatin AUC versus the plasma concentrations at two sampling times indicated that the addition of the end-of-infusion concentration slightly increased the precision of AUC estimation. The best two-sample model was:

$$AUC_{LSM} = 0.0668 * C_{120\,\mathrm{min}} + 0.391 * C_{240\,\mathrm{min}}, \quad r = 0.999$$

where $C_{120\mathrm{min}}$ and $C_{240\mathrm{min}}$ are the carboplatin concentrations (mg/l) at 120 and 240 min from the start of the infusion.

The one-point LSM was validated by splitting the data into two sets. The original 44-patient dataset was split equally into modeling-building and validation datasets. Split of the data was made at random using the S-plus program. The first set, called the model-building set, was used to develop the one-point LSM model. The second dataset, called the validation set, was used to evaluate the reasonableness and predictive ability of the

Table 4. Frequency of each covariate entering best GAM model using a bootstrap method

Covariate	Frequency entering CL	Frequency entering V1	Frequency entering Q	Frequency entering V2
SCR	0.73	0.18	0.52	0.19
WT	0.64	0.67	0.08	0.03
TBIL	0.32	0.52	0.16	0.48
LDH	0.21	0.11	0.22	0.49
BSA	0.15	0.26	0.16	0.23
ALB	0.14	0.49	0.70	0.56
PT	0.08	0.01	0.05	0.26
AGE	0.04	0.36	0.38	0.22
OT	0.04	0.01	0.14	0.14
HT	0.01	0.07	0.19	0.14

Table 5. Bootstrap validation of final population model of high-dose carboplatin

Parameter	Final model – original data				Bootstrap models	
	Mean	SD	Random effect (ω^2)	SD of ω^2	Mean	SD
CL (l/min)	0.101	0.004	0.045	0.0137	0.102	0.005
V1 (l)	15.5	0.43	0.0191	0.00887	15.6	0.44
Q (l/min)	0.0132	0.0013	0.107	0.0482	0.0129	0.0016
V2 (l)	7.07	0.558	0.244	0.0961	7.30	3.22
Residual, σ^2	0.0248	0.00414				

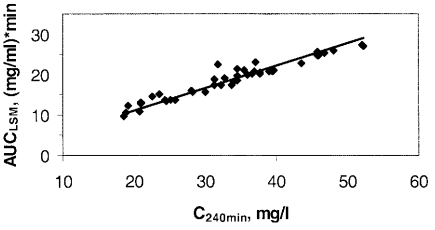

Fig. 3. Single-point LSM showing relationship between AUC and the carboplatin plasma ultrafiltrate concentration at 240 min. Regression line: $y = 0.533x$ ($r = 0.998$)

selected model. The resultant LSMs were in close agreement with the LSM obtained with all 44 patients.

For model – building data,

$$AUC_{LSM} = 0.5531 * C_{240\,\mathrm{min}},$$

$$r = 0.998, \text{standard error of slope} = 0.0071$$

For validation data,

$$AUC_{LSM} = 0.5529 * C_{240\,\mathrm{min}},$$

$$r = 0.997, \text{ standard error of slope} = 0.0093$$

Comparison of population model, LSM and Calvert formula dosing approaches

Figure 4 provides a comparison of the different means to estimate a patient's actual AUC. Two population model-based approaches were used, one based on the TVCL (i.e. final population model), and the other utilized a Bayesian estimation given each patient's measured carboplatin concentrations. The regression equations were: $AUC_{Actual} = 1.013AUC_{Bay}$ ($R^2 = 0.943$) for the Bayesian methods, and $AUC_{Actual} = 0.981AUC_{TVCL}$ ($R^2 = 0.226$) for the TVCL-based method. The fitted equation for the LSM approach was $AUC_{Actual} = 1.017\ AUC_{LSM}$ ($R^2 = 0.874$). The Calvert approach, $AUC_{Calvert}$, did not appear to correlate with AUC_{Actual}.

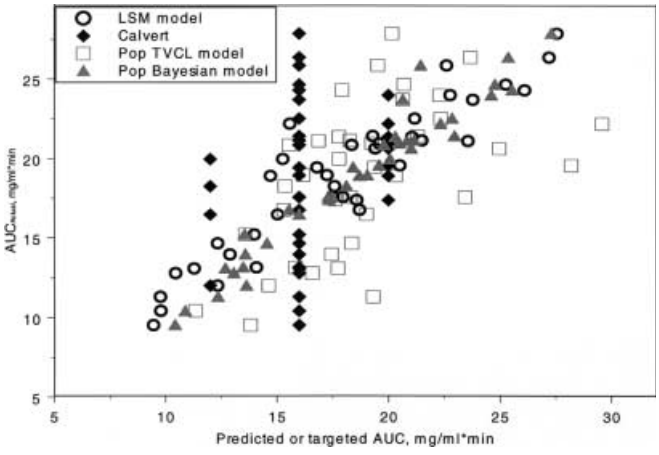

Fig. 4. Comparison of patient AUC values obtained by two population model approaches, a single-point LSM approach ($AUC_{LSM} = 0.553*C_{240min}$) and the Calvert formula ($AUC_{Calvert}$) with the actual AUC (AUC_{Actual}). The two population approaches were the Bayesian approach (AUC_{Bay}) and the final population model (AUC_{TVCL}). See the text for the regression equations

Discussion

Population-based pharmacokinetic models are increasingly being used in clinical pharmacology to characterize drug disposition in large populations. A fundamental goal is to provide a quantitative platform to assess if and in what manner a patient's covariates impact on the drug's pharmacokinetics. Through these types of analyses, specific dosing guidelines and algorithms are sought for subpopulations and individuals, respectively. The current study used data from 44 ovarian cancer patients who participated in two different phase I trials of combination chemotherapy that incorporated high-dose carboplatin chemotherapy. This was the first population-based analysis of high-dose carboplatin chemotherapy, although a number of population-based models have been developed for standard doses of carboplatin [5, 6]. Prior pharmacokinetic analyses had established that the pharmacokinetics of carboplatin are linear up to doses of 450 mg/m^2 [8, 18, 24]. Further, it has been shown that renal clearance, primarily due to glomerular filtration, of carboplatin is extensive with about 50% to 70% of the total administered dose excreted in urine in the first 24 h [8, 18, 22, 24]. In the absence of a population-based analysis of high-dose carboplatin, the goal of the current investigation was to apply such a pharmacokinetic strategy to determining the influence of patient covariates on carboplatin's pharmacokinetics in this unique patient population.

Development of the final population model for high-dose carboplatin utilized three distinct steps. Completion of step 1 resulted in the identification of the best structural model as being a linear two-compartment

model with interpatient and intrapatient variability described by exponential and constant coefficient of variance models, respectively.

In the covariate screening step, a GAM protocol was used to identify candidate covariates for each pharmacokinetic parameter. The separate GAM procedure has been used as an intermediate step between the development of the covariate-free model and final population model to reduce the scope of the problem of identifying significant covariate-pharmacokinetic parameter relationships. In the current analysis, GAM reduced the number of covariates from ten to no more than three for any parameter. GAM indicated that all covariates had a linear relationship with each pharmacokinetic parameter except for a nonlinear relationship between WT and CL. The GAM analysis tends to be more permissive than the final population model in terms of selecting significant covariate-pharmacokinetic parameter relationships. This potential difference is also dependent on the criteria for covariate inclusion used in step 3. In our backward deletion approach, a covariate was only included if the NONMEM objective function increased by 10.8 ($P < 0.001$) upon removal of a covariate, which is quite restrictive. Hence, the GAM analysis served as a valuable screening procedure to expedite the development of the final population model.

Both the GAM and final population model selected WT and SCR as significant covariates for CL. It was not surprising to find SCR as a significant covariate for CL because carboplatin undergoes primary renal excretion and SCR is a measure of renal function. The variability of carboplatin clearance is widely accepted and has been largely attributed to alterations in renal function. Other population pharmacokinetic models at standard carboplatin doses [5] have also incorporated serum creatinine in the covariate structure. Identification of WT as a covariate reflects the dependency of renal clearance, via the Calvert formula, on creatinine clearance and implicitly on body weight.

WT was also a significant covariate on the volume of distribution of the central compartment and reflects an increase in physiological or distributional spaces available to unbound carboplatin as weight increases. Since plasma protein binding of carboplatin is considered to be moderate or low [8, 18, 24], greater values of V_1 suggest greater tissue protein binding or partitioning of unbound drug. TBIL was identified in the GAM analysis for V_1; however this was not the case when it was examined by the backward deletion method in the population model. There is no obvious explanation of how TBIL concentrations or hepatic function, could significantly impact on carboplatin's volume of distribution. Based on the aforementioned fact that carboplatin does not appreciably bind serum albumin it was somewhat surprising that ALB was significantly related to both the distributional clearance, Q, and volume of the peripheral compartment, V_2. It seems plausible that covariate-pharmacokinetic relationships are detected in the GAM analysis in the absence of obvious physiological and pharmacological justifications.

The final population model obtained by a backward deletion protocol did predict the observed ultrafiltrate carboplatin concentrations accurately (see Fig. 1). Agreement between the TVCL and the true clearance obtained by Bayesian parameter estimation was moderate (see Fig. 2), and indicated that additional patients may be required to improve the model further. It is each patient's TVCL value that would be used in the design of a high-dose carboplatin dosage regimen. A prospective study design with a limited blood sampling schedule could provide the necessary data to revise the current model. The limited number of patients receiving high-dose chemotherapy directed us to use a bootstrap validation method for the current model. In both instances in which a bootstrap procedure was applied (Tables 4 and 5) excellent agreement was obtained between the original and bootstrap datasets for both the covariate structure and final model parameters. It was also noted that the high-dose population model had many features analogous to the population model derived from standard-dose carboplatin models [5, 6].

LSMs have been used as a simple means to collect pharmacokinetic information that can be incorporated into the design of drug dosing regimens. A LSM can be viewed as an alternate technique to the population modeling approach in the context of dosage regimen design. In lieu of a population model, the LSM requires one to two drug concentration measurements to indicate a dose to achieve the desired endpoint, typically an AUC value. The population model is more powerful in that it can be used, via the TVCL equation, to determine the first dose, and with additional drug concentration measurements provide Bayesian estimated pharmacokinetic parameters. It was seen that this latter approach (AUC_{Bay}) provided the most accurate estimate of each patient's measured AUC (see Fig. 4). In fact, both this method and the LSM, methods that require actual drug concentrations, did provide accurate predictions of the patient's AUC values. The population model-based TVCL estimation of the measured AUC values was not as accurate as the concentration-dependent methods, yet it can be used to design a regimen for the first dose or whenever measured patient plasma drug concentrations are unavailable. The LSM provides a manageable alternative when population modeling expertise is unavailable.

A number of LSMs for high-dose carboplatin have been developed [19, 23, 25] to predict AUC. For the high-dose carboplatin models, single concentration point regression models have been derived and assessed for validity. Although the combination regimens differed, the LSM based on a single sample at 2.75 h [23, 25] following a 1-h infusion was more precise than a LSM based on a 24-h plasma concentration [19]. The LSM derived for high-dose carboplatin in the current investigation is consistent with the model of Sorensen et al. [23] in that carboplatin concentrations at a

relatively short time (240 min, 2 h after the end of a 2-h infusion) yielded the most accurate LSM (see Fig. 3). It was subsequently validated using cross-validation within the studied population of 44 patients; however, a prospective evaluation to increase the sample size would be desirable.

In conclusion, we developed both a population pharmacokinetic model and LSM for high-dose carboplatin treatments that was a component of high-dose combination chemotherapeutic regimens. In both cases, the models performed well when analyzed in the contexts of the retrospective and bootstrap analyses. Prospective studies in ovarian cancer patients should be conducted to further evaluate the current models and revise them as required.

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