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ORIGINAL ARTICLE

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Population pharmacokinetics of cisplatin in adult cancer patients

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Abstract *Purpose*: To characterize the pharmacokinetics of the anticancer agent cisplatin, and explore the influence of patient covariates and interoccasion variability on drug disposition. *Methods*: Data were obtained from 285 patients (519 complete curves; 3483 plasma samples) who received the drug as a 3-h intravenous infusion at a mean dose of 144 mg (range 75–210 mg). The population model was built with the use of NONMEM, performing generalized-additive modeling to identify candidate covariates including body-surface area (BSA), age, sex, height, weight, hematocrit, total protein, albumin, serum creatinine, and creatinine clearance, and using a backward deletion protocol to obtain the final models for clearance (CL) and volume of distribution (V). *Results*: The final model was a one-compartment linear model with BSA (in meters squared) as the only significant covariate that impacted on both CL and V: TVCL (in liters per hour) = 51.7 + 26.3×(BSA − 1.855) and TVV (in liters) = 41.1 + 24.6×(BSA − 1.855), where TVCL and TVV are referred to as typical values that could be used a priori in dosage regimen design. The interindividual and interoccasion variability estimates for CL and V were 16.82 and 20.35%, and 13.93 and 22.91%, respectively. *Conclusion*: A population pharmacokinetic model for cisplatin has been developed that incorporates measures of body size to predict clearance. In this patient population, cisplatin pharmacokinetics were not associated with age, sex, or measures of renal dysfunction.

Keywords Cisplatin · Population model · Pharmacokinetics

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Introduction

Cis-diamminedichloroplatinum (cisplatin) is a commonly used anticancer drug with a broad spectrum of activity against malignant solid tumors, including lung, head and neck, bladder, germ cell, ovarian, endometrial, and cervical cancer [5]. In the conventional 3-weekly or 4-weekly treatment regimens, dose-limiting side effects include renal tubular dysfunction, peripheral neuropathy, and hearing loss (ototoxicity), whereas hematological toxicity becomes dose limiting in the more dose-dense, weekly regimens [23]. Nausea and vomiting—once predominant side effects of cisplatin—have become manageable with a combination of dexamethasone and 5-hydroxytryptamine-3 receptor antagonists [5, 17, 23].

Although cisplatin-induced toxicity is dose-dependent, the individual susceptibility to side effects varies considerably. As for most other anticancer agents, the administered dose of cisplatin is normalized by a patient's body surface area (BSA). However, for most anticancer agents clearance is poorly correlated to body-size measures and hence, the routine use of BSA as the only independent variable considered in drug dosing is questionable [3, 6, 16]. Previous studies have revealed significant relationships between cisplatin pharmacoki-

netics and the likelihood of tumor response and toxicity [29]. Hence, availability of a useful model incorporating factors affecting drug clearance that could be used to predict or adapt appropriate doses of cisplatin is required.

Standard noncompartmental pharmacokinetic evaluation has demonstrated that exposure to cisplatin is dose-proportional over a wide dose range [16]. We have also shown that cisplatin disposition is unaffected by concomitant administration of the chemotherapeutic agents etoposide [29], docetaxel [24], irinotecan [12–14], and topotecan [4, 15]. The data from these trials were collected prospectively to characterize the pharmacokinetics of cisplatin in a broad patient population under general clinical conditions. Here, we report the population pharmacokinetic model-building process, and the exploration for demographic subpopulations for which dose adjustment may be needed.

Materials and methods

Patient eligibility

All patients studied had a confirmed diagnosis of a malignant solid tumor and were entered in five different clinical phase I trials [4, 13, 15, 24, 29], with cisplatin given alone or as part of a combination chemotherapy regimen. According to the inclusion criteria of these trials, all patients were 18–75 years of age with an Eastern Cooperative Oncology Group performance status 0–2, had had no previous anticancer therapy for at least 4 weeks, and had adequate hematopoietic (absolute neutrophil count ≥1500/μl and platelet count ≥100,000/μl), hepatic (total serum bilirubin not more than 1.25 times the upper limit of institutional normal values and serum transaminase levels not more than 2.5 times the upper limit of institutional normal values or not more than five times in the case of liver metastases), and renal function (normal serum creatinine and/or creatinine clearance ≥60 ml/min) at the time of study entry. None of the patients used any other comedication known to interfere with cisplatin pharmacokinetics. All patients were treated at the Erasmus MC—Daniel den Hoed Cancer Center (Rotterdam, The Netherlands), the study protocols were reviewed and approved by the Erasmus MC review board, and patients gave written informed consent to participate. The overall safety, tolerability, and efficacy results and a traditional pharmacokinetic analysis have been reported in detail previously [4, 12–15, 24, 29].

Drug administration

Cisplatin powder (Pharmachemie, Haarlem, The Netherlands) was dissolved in 250 ml of a sterile, hypertonic solution containing 3% (w/v) sodium chloride and was administered as a 3-h continuous intravenous infusion at doses ranging from 50 to 100 mg/m^2 with treatment cycles repeated every week or every 3 weeks. Antiemetic prophylaxis consisted of a 5-hydroxytryptamine-3 receptor antagonist in combination with dexamethasone. For prevention of cisplatin-induced renal toxicity, a standard prehydration infusion with 1 l normal isotonic 0.9% (w/v) sodium chloride or 5% (w/v) dextrose/0.9% (w/v) sodium chloride (1:1, v/v) was used, as well as a posthydration regimen of 3 l of the same solution containing potassium chloride (20 m *M*) and magnesium sulfate (2 g/l). Diuretics were not administered routinely.

Sampling and drug analysis

Since the nonprotein-bound drug fraction is considered to be the pharmacologically active component, we focused on measurement of unbound cisplatin concentrations. All analytical measurements were performed at the Laboratory of Translational and Molecular Pharmacology of the Erasmus MC—Daniel den Hoed Cancer Center using a validated assay based on ethanolic protein precipitation followed by atomic absorption spectrometry (lower limit of quantitation 0.005 μg/ml) [13]. A previous direct comparison of this technique with the more routinely used methods based on ultrafiltration revealed that the recovery of unbound cisplatin observed for ethanol-treated samples was not significantly different from that recorded for sample preparation using ultrafiltrates [18].

Blood samples were drawn from the arm opposite to the infusion site and collected in 4.5-ml glass tubes containing lithium heparin as anticoagulant. Samples were collected immediately before drug infusion, at 1 and 2 h after the start of infusion, at 5 min before the end of infusion, and at 0.5, 1, 2, 3, and 18 h after the end of infusion. In a limited number of patients, additional samples were obtained at 1.5 and 5 h after the end of infusion. Plasma was separated by centrifugation at 3000 *g* for 10 min, and 500-μl aliquots of plasma were immediately extracted with 1000 μl neat ice-cold (−20°C) ethanol in a 2-ml polypropylene vial. After a 2-h incubation at −20°C, the supernatant was collected by centrifugation at 23,000 *g* for 5 min at 4°C and transferred to a clean vial. A volume of 600 μl was evaporated to dryness under nitrogen at 60°C, and the residue was reconstituted in 200 or 600 μl water containing 0.2% (v/v) Triton X-100 and 0.06% (w/v) cesium chloride by vigorous mixing for 10 s. A volume of 20 μl was eventually injected into the flameless atomic absorption spectrometer. Samples were analyzed for platinum-containing species with a Perkin Elmer 4110 ZL spectrometer (Perkin Elmer, Norwalk, Ct.) with Zeeman background correction using peak area signal measurements at a wavelength of 265.9 nm and a slit width of 0.7 nm. The injection temperature was set at 20°C. Drug concentrations were determined by interpolation on linear calibration curves constructed from blank (drug-free) human plasma obtained from healthy volunteers by a linear least-squares regression analysis using a

weight factor of $1/X^2$. The mean percentage deviation from nominal values (accuracy) and precision (within-run and between-run variability) were always less than 15%.

Pharmacokinetic model

Population pharmacokinetic analysis was performed with the population mixed-effect modeling computer program NONMEM (version V with double precision; S.L. Beal and L.B. Sheiner, University of California, San Francisco, Calif.). Development of the population model was performed in three distinct steps [19], as follows: (1) development of an initial covariate-free model using the first-order conditional estimation method within NONMEM and Bayesian estimation of individual pharmacokinetic parameters; (2) evaluation of the influence of patient characteristics; and (3) optimization of the final model.

The database incorporated all cisplatin samples collected during the study protocols. The pharmacokinetic parameters estimated were clearance (CL) and volume of distribution (V). Interpatient variability (η) and residual or intrapatient variability (ϵ) were evaluated through alternate statistical models (i.e., additive, constant coefficient of variation, and exponential). Interoccasion variability (IOV; i.e., the variability between the different occasions) was considered as well since a substantial number of patients underwent pharmacokinetic sampling on more than one treatment cycle, and it is obvious that pharmacokinetic parameters may vary randomly between study occasions. Therefore, ignoring IOV could result in biased population parameter estimates and the selection of inappropriate models for population data. Identification of the best structural model was based on the objective function value from NONMEM output and on interpretation of diagnostic plots of weighted residuals vs predicted unbound cisplatin concentrations.

After the initial model was selected, empirical Bayesian estimates of the individual pharmacokinetic parameters were calculated (post hoc step in the NONMEM program). The effect of patient characteristics on the variables CL and V was then evaluated using generalized-additive modeling (GAM) [9], which was performed with Xpose (version 2.04) running within the S-plus (version 2000) program, as well as by graphical examination. BSA, age, sex, height, weight, hematocrit, total protein, albumin, serum creatinine, and calculated creatinine clearance were evaluated by analysis of the relationship between the patient variable or covariate and the empirical pharmacokinetic estimate using Akaike's information criterion (AIC) [1]. An individual covariate was considered to significantly improve the model if the difference in objective function values between models was greater than 3.84. All significant covariates were added to the model and then removed one at a time in order of decreasing improvement in AIC, and only those that showed a significant contribution to the fit were considered and retained in the model. The recorded covariates were updated when pharmacokinetic data in successive cycles were modeled. During this step, the level of statistical significance was chosen at $P < 0.001$, corresponding with a greater than 10.83 increase in the objective function value ($-2 \times$ the log likelihood function). Finally, model performance was assessed by graphic plots of (1) observed vs predicted unbound cisplatin plasma concentrations and (2) weighted residuals vs predicted unbound cisplatin plasma concentrations randomly scattered around zero. This analysis was done with the software package JMP, version 3.2.6 (SAS Institute, Carey, N.C.).

Results

Patient population

The patient characteristics are summarized in Table 1. A total of 519 treatment cycles from 285 patients were available for pharmacokinetic analysis. Of the 285 patients, 140 were also evaluated during a second treatment cycle, and 94 during a second and third cycle. The patients were treated with cisplatin given either alone (34 patients, 12%) or as cisplatin-based combination therapy with oral etoposide (76 patients, 27%), intravenous docetaxel (61 patients, 21%), intravenous irinotecan (57 patients, 20%), or oral topotecan (57 patients, 20%). Cisplatin was administered at doses ranging from 50 to 100 mg/m^2 (mean dose 144 mg, range 75–210 mg), with treatment cycles repeated every week (93 patients, 33%) or every 3 weeks (192 patients, 67%).

Initial parameter estimates

Samples obtained beyond 12 h after the start of cisplatin administration were all below the lower limit of quan-

Table 1 Patient demographics at baseline in cycle 1. Continuous data are given as median with range in parentheses, and categorical data as number of patients with percentage of the total population in parentheses

Characteristic	Value
No. of patients studied	285
No. of evaluable courses	519
Sex	
Female	112 (39%)
Male	173 (61%)
Age (years)	54 (21–74)
Height (m)	1.73 (1.28–1.92)
Weight (kg)	72.5 (39.3–115)
BSA (m^2)	1.85 (1.29–2.40)
Infusion duration (h)	3.00 (2.00–4.00)
Hematocrit (l/l)	0.39 (0.27–0.50)
Albumin (g/dl)	4.20 (2.50–5.50)
Total protein (g/dl)	7.40 (5.60–9.20)
Serum creatinine (μM)	84 (52–146)
Creatinine clearance (ml/min)	76.2 (39.3–156)

titation of the analytical method. The final data set consisted of 4643 plasma samples, of which 3483 had concentrations with a value above the lower limit of quantitation of the analytical assay. The remaining 1160 samples were not used in the modeling analysis. The observed plasma concentrations of unbound cisplatin are shown in Fig. 1. Development of the structural covariate-free model indicated that a linear, open one-compartment model best fitted the observed concentration–time data. Monoexponential and biexponential declines were both tried, but the data did not support a more complex model because of the high correlation between model parameters and the large standard error in model estimates.

Interpatient variability (η) for CL and V was modeled by a constant coefficient of variation in this best-fit structural model as follows:

$$\mathrm{CL} = \mathrm{TVCL} \times (1 + \eta_{\mathrm{CL}})$$

$$V = \mathrm{TVV} \times (1 + \eta_{V})$$

In these equations, CL and V are empirical Bayesian parameter estimates based on population values combined with the observed individual values for CL and V, respectively. TVCL and TVV are typical values for CL and V, respectively, which are determined from the population mean parameters; η_{CL} and η_{V} are measures of the difference between CL and TVCL, and V and TVV, respectively.

Residual or intrapatient variability (ϵ_{ij}) is a random variable assumed to have a population mean of zero. It was modeled as an additive term in the best-fit structural pharmacokinetic model ($\mathrm{Y} = \mathrm{F} + \epsilon_{\mathrm{ij}}$), and accounts for differences in observed and model-predicted unbound cisplatin concentrations in the individual patient. A combined additive and proportional residual error model was also tested, but it did not improve the model fit. As mentioned earlier, blood sampling was obtained during one (OCC1), two (OCC2), or three (OCC3) treatment cycles per patient. The model for IOV for CL (π_{CL}) and V (π_{V}) was modeled as follows:

$$\mathrm{CL} = \mathrm{TVCL} \times \exp\left[\eta(1) + \eta(3) \times \mathrm{OCC1} + \eta(5) \times \mathrm{OCC2} + \eta(7) \times \mathrm{OCC3}\right]$$

$$V = \mathrm{TV} \times \exp\left[\eta(2) + \eta(4) \times \mathrm{OCC1} + \eta(6) \times \mathrm{OCC2} + \eta(8) \times \mathrm{OCC3}\right]$$

in which $\eta(1)$ is the interpatient variability in CL; $\eta(3)$, $\eta(5)$ and $\eta(7)$ the IOV in CL for occasions 1, 2 and 3; $\eta(2)$ the interpatient variability in V; and $\eta(4)$, $\eta(6)$ and $\eta(8)$ the IOV in V for occasions 1, 2 and 3.

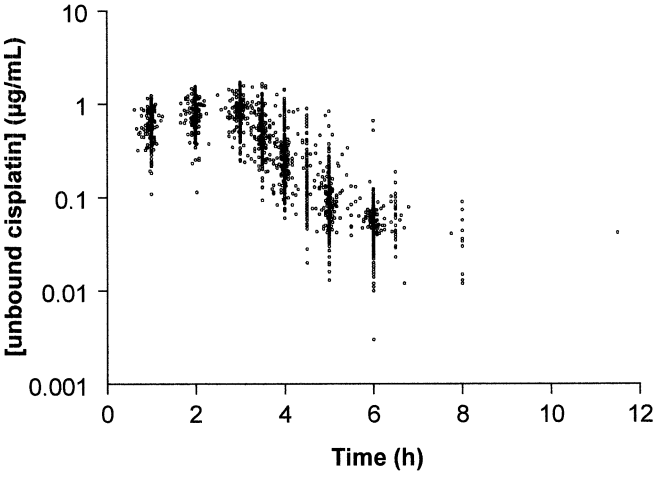

Fig. 1 Observed plasma concentrations of unbound cisplatin after intravenous infusion of cisplatin to 285 patients (519 courses)

Demographic covariates and final model

The GAM analysis identified BSA, hematocrit, and sex as candidate covariates influencing CL, whereas BSA and albumin were identified as candidate covariates influencing V. Concomitant medication (etoposide, docetaxel, irinotecan, and topotecan) was also evaluated as a potential covariate, but it was not selected as statistically significant and, hence, was not included in the final model. Eventually, both for CL and V, only BSA was maintained as a significant covariate in the final population pharmacokinetic model for cisplatin, as follows:

$$\mathrm{TVCL(l/h)} = (51.7 \pm 0.659) + (26.3 \pm 3.55) \times (\mathrm{BSA} - 1.855)$$

$$\mathrm{TVV(l)} = (41.4 \pm 0.764) + (24.6 \pm 4.15) \times (\mathrm{BSA} - 1.855)$$

The decrease in objective function value from the covariate-free model to the final model was 61, and resulted in values for interindividual coefficient of variation in CL and V of 19.5% and 23.5%, respectively. The predicted concentrations of unbound cisplatin (in the range of 0.005–1.30 µg/ml) in relation to the observed data are shown in Fig. 2. Although the model tended to underestimate concentrations above 1.30 µg/ml, data in this range represented only a minor proportion of the full data set (49 out of 3483, 1.41%). The overall regression equations are given by:

$$Y = (0.9785 \pm 0.00852)X + (0.0252 \pm 0.00487)$$
$$(\text{population predictions};\ R^2 = 0.791)$$

$$Y = (0.9977 \pm 0.00419)X + (0.0209 \pm 0.00250)$$
$$(\text{individual predictions};\ R^2 = 0.942)$$

In the population predictions, the residuals (i.e., the difference between the observed and final model-predicted concentrations) had a mean ($\pm$SD) value of 0.015 ± 0.167 µg/ml, with 90% of the residuals ranging from -0.172 to 0.209 µg/ml ($P > 0.99$ vs hypothesized mean = 0; Fig. 3).

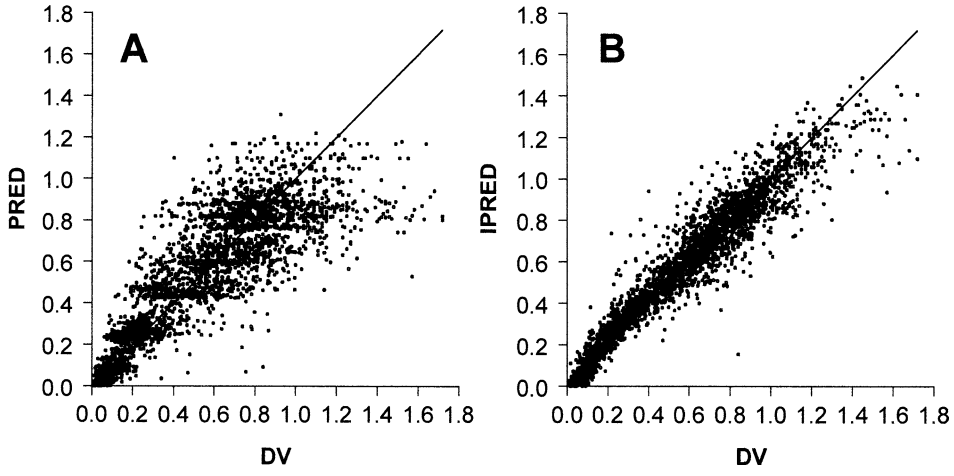

Fig. 2a, b Observed concentrations (DV, dependent variable) vs the population predictions (PRED; **a**) and individual predictions (IPRED; **b**) of unbound cisplatin. All concentration units are micrograms per milliliter. The *solid lines* indicate the lines of identity

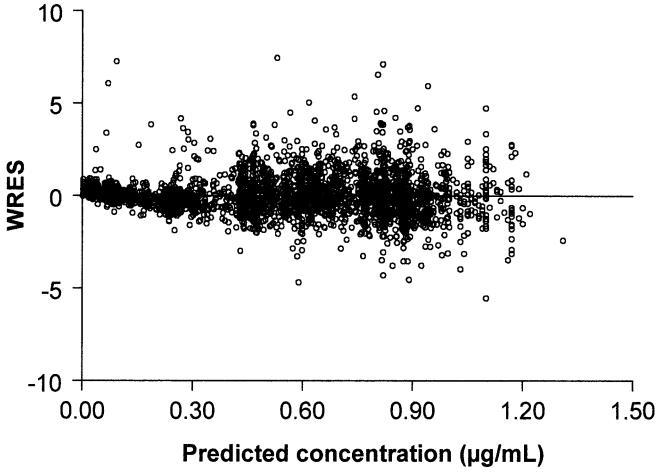

Fig. 3 Weighted residuals (WRES) vs the predicted concentrations of unbound cisplatin

The clearance and volume of distribution of unbound cisplatin for a representative patient with a BSA of 1.855 m^2 were 51.7 l/h and 41.4 l, respectively. After accounting for the covariate of BSA, the remaining interindividual variability for clearance was 16.82%. A summary of the variability estimates, including values for residual variance (σ^2), is given in Table 2.

Discussion

The present study was initiated through the results of a previous study on the relationship between cisplatin exposure and BSA, which demonstrated a significant correlation between the plasma clearance of unbound cisplatin and BSA. However, the magnitude of this correlation was considered insufficient to justify BSA-guided dosing of cisplatin [16]. This is not surprising if one considers the rather complex pharmacological behavior of cisplatin, which includes several processes that are unlikely to be dependent on BSA. During and shortly after intravenous administration of cisplatin, rapid renal excretion of unbound cisplatin takes place at a clearance rate approximately five to ten times the glomerular filtration rate, suggesting that unbound cisplatin is excreted by the kidneys through an active tubular secretion process. However, only 20–35% of the administered dose can be retrieved in the urine during and after drug administration [22, 28]. This could be explained by progressive, strong and partially irreversible binding to plasma proteins (mainly albumin), whereas binding to cellular proteins and nucleic acids also occurs [11]. Protein binding and cellular toxicity are further influenced by the equilibrium between chlorinated and hydrated platinum species, the hydrated platinum compounds being more reactive and producing more cellular toxicity (especially renal tubular toxicity) [7].

Although exposure to cisplatin reflected by the area under the plasma concentration–time curve (AUC) of unbound platinum is highly variable, a close correlation has been demonstrated between in vivo DNA adduct formation in leukocytes and AUC. Furthermore, AUC and DNA adduct formation are significantly higher in patients with tumors responding to treatment than in patients not responding [28]. In view of this, and because

Table 2 Summary of variability estimates (*CL* clearance; *V* volume of distribution, η_{CL} and η_V interindividual variability for CL and V, respectively; π_{CL} and π_V IOV for CL and V, respectively; $R(\eta)$ correlation between η_{CL} and η_V; $R(\pi)$ correlation between π_{CL} and π_V; σ^2 residual variance, *SE* standard error expressed in the coefficient of variation)

	η_{CL} (%)	η_V (%)	π_{CL} (%)	π_V (%)	R(η) (%)	R(π) (%)	σ^2
Estimate	16.82	20.35	13.93	22.41	0.859	0.343	0.00989
SE	6.78	9.31	5.06	9.99	7.10	5.30	0.000698

AUC is determined by administered dose and drug clearance, we evaluated the influence of a number of patient variables (i.e., age, sex, hematocrit, total protein, albumin, serum creatinine, creatinine clearance) in addition to common measures of body size (i.e., height, weight, BSA) on unbound cisplatin pharmacokinetics in a nonlinear mixed-effect model.

The population pharmacokinetic modeling was based on 519 cisplatin treatment cycles in a group of 285 patients. The best structural covariate-free model was a linear one-compartment model with a constant coefficient of variation error model for interpatient variability and an additive error model for intrapatient variability. Since a total of 140 patients had blood sampling on two or three occasions, IOV was also taken into account. IOV could be successfully modeled through an exponential error model, which helped in the selection of appropriate models for the population pharmacokinetic data.

Common anthropomorphic covariates were not found to influence cisplatin disposition to a clinically relevant extent, and BSA was identified as the only significant covariate on clearance and volume of distribution. This finding is in accordance with the two previous population pharmacokinetic studies presented by Hanada et al. in 27 patients (dose 60–100 mg/m^2 over 90 min) [8] and Nagai et al. in 26 patients (dose 80 mg/m^2 over 2, 3.5, or 4 h) [21]. The latter study also demonstrated that unbound cisplatin clearance is schedule dependent, with clearance increasing with a decrease in infusion duration, in line with earlier observations [26, 27]. In the present study, cisplatin was administered as a 3-h infusion, and the infusion duration was constant within each patient. Height and weight had no additional value to BSA in the population model for cisplatin. It is noteworthy that, although there was a statistically significant influence of BSA on cisplatin clearance, the relationship was very shallow and the data showed considerable scatter. Specifically, cisplatin clearance increased by only 2.63 l/h per one-tenth unit of body size and hence, a 0.10-m^2 increase in BSA was associated with a mere 5.09% increase in clearance. The interquantile range of BSA values observed in our patient population was 1.71–2.00 m^2, which suggests that 75% of treated adults will have a predicted cisplatin clearance in the range 47.9–55.5 l/h. This range is clearly of very minor relevance against a background of interindividual variability in clearance of 17%. A similar argument can be made for the influence of BSA on the volume of distribution, suggesting that dose adjustment of cisplatin for body size measures appears unnecessary. An exception would be the treatment of patients at extremes of BSA, such as those observed in our group. As predicted by the population model, average 1.29-m^2 and 2.40-m^2 patients would have clearances of 36.0 l/h and 66.0 l/h, respectively, which translate into a twofold difference in systemic exposure to unbound cisplatin for a given intravenous dose.

Age had no significant influence on unbound cisplatin clearance, which is in line with reports describing a lack of age-dependent cisplatin nephrotoxicity [10, 31]. Although, on average, women have a 15% smaller unbound cisplatin clearance than men [16], the addition of sex into the final population model did not result in substantial improvement. Hematocrit, total protein and albumin were introduced into the model because a relationship with unbound drug clearance and volume of distribution was expected. Namely, during and after intravenous administration of cisplatin, progressive protein binding takes place mainly involving albumin but also other plasma proteins and intracellular proteins such as hemoglobin. However, addition of these covariates to BSA did not lead to improvement of the model. The same applies to serum creatinine and creatinine clearance, although this could partly be explained by the fact that patients with moderate or severe renal dysfunction were excluded from the study protocols. Patients with moderate to severe renal impairment demonstrate aberrant pharmacokinetic profiles [25], and unbound cisplatin peak concentrations in such patients (above 2.0 μg/ml) have been linked to several markers of cisplatin-associated nephrotoxicity [2, 20]. In our population, model-predicted peak concentrations (median 0.912 μg/ml, range 0.266–1.49 μg/ml) were not related to pretherapy serum creatinine values, creatinine clearance, or the maximum percent decrease in creatinine clearance (median 2.61%, range −36.6 to 38.1%; $n = 91$ patients) following repeat administrations (not shown). The relatively low peak levels and the applied prehydration and posthydration regimens likely contributed to the lack of significance in these relationships.

The final parameter estimates from the current population analysis approximate the average pharmacokinetic parameters of more traditional analyses, with mean clearance values of 51.7 l/h vs 56.3 l/h (range 31.0–123 l/h; $n = 391$ patients; reference 16 and unpublished data), respectively. The smaller range of observed clearance values than those seen in the previous study, albeit in a similar patient population, is likely related to the present analysis representing a more robust modeling that was less influenced by sampling, analytical and/or dosing errors. After BSA as covariate was accounted for, the remaining interindividual variability for clearance was moderate at approximately 17%. At present, the causes for this variability are unknown. In as much as cisplatin clearance is primarily dictated by near-covalent binding to serum proteins and renal elimination pathways, the variability may reflect, in part, kinetic processes that remain undetected by the analytical procedure employed, which is based on simultaneous measurement of all platinum-containing species.

In conclusion, the current population analysis confirms a number of findings previously described by conventional pharmacological analyses [16]. In particular, values for CL agreed with those reported previously, and BSA was a significant covariate as suggested by other population models with smaller numbers of patients [8, 21]. The current modeling efforts also, through the covariate analysis, have eliminated other

candidate covariates from further consideration as important determinants of cisplatin disposition. It is difficult to make specific recommendations for dosing changes of cisplatin-containing chemotherapeutic regimens on the basis of the current findings. In spite of the low interindividual variabilities in cisplatin CL and V, monitoring of unbound cisplatin plasma levels and dosage adjustment may be necessary to optimize cisplatin efficacy in cancer patients [30], although therapeutic drug monitoring of cisplatin is currently not routinely available. However, the described population pharmacokinetic model further increases our knowledge on this clinically important drug, and provides the basis for designing future, prospective investigations aimed at refining the model and evaluating alternative and improved cisplatin dosing regimens.

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