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Evaluation of formulas using the serum creatinine level to calculate the optimal dosage of carboplatin

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Abstract. Carboplatin is a chemotherapeutic agent frequently used in the treatment of various malignancies. An individual dosing strategy has been recommended to yield the most optimal exposure, expressed as the area under the concentration-time curve (AUC). The formula developed by Calvert et al. (dose = target-AUC × [GFR + 25]) can be used to achieve this. However, due to the inconvenient [^{51}Cr]-ethylenediaminetetraacetic acid ([^{51}Cr]-EDTA)-based measurement of the glomerular filtration rate (GFR), its application in the clinic has thus far been limited. Chatelut and co-workers have recently proposed a formula to estimate carboplatin clearance using the serum creatinine concentration. We retrospectively tested the Chatelut equation and the Calvert formula using either the creatinine clearance based on 24-h urine collection or the creatinine clearance based on the formula of Cockcroft and Gault. The latter equations were shown to predict the carboplatin clearance reasonably well, although systematic overprediction and underprediction occurred. However, the formula proposed by Chatelut and co-workers had no significant bias and was precise. It is proposed that this formula be used to calculate the optimal carboplatin dosage after prospective validation has been performed.

Key words AUC · Carboplatin · Pharmacokinetics

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Introduction

Carboplatin [*cis*-diammine (1,1-cyclobutanedicarboxylato)platinum(II), CBDCA, JM8, NCS-241240, Paraplatin] is a second-generation platinum-containing compound with proven activity against a range of malignant solid tumors [20]. Carboplatin is much less nephrotoxic, neurotoxic, and emetogenic than its parent compound cisplatin [18]. Its dose-limiting toxicity is myelosuppression, particularly thrombocytopenia.

The pharmacokinetics of carboplatin, especially the area under the concentration versus time curve (AUC), vary considerably among patients, mainly due to interindividual variation in renal function. Furthermore, it has been demonstrated that this measure of drug exposure is highly correlated with the degree of myelosuppression [7, 10, 12, 13, 20] and with the response rate [10]. The close relationship between carboplatin clearance and the glomerular filtration rate (GFR) [16, 19, 20] has led to the development of a formula that allows the calculation of the dosage that results in a certain (target) AUC [2]. This formula, known in the literature as the Calvert formula, is: Dose (mg) = target AUC × (GFR + 25). In this formula, the GFR (expressed in milliliters per minute) is based on the [^{51}Cr]-ethylenediaminetetraacetic acid ([^{51}Cr]-EDTA)-based determination of clearance. Calvert et al. [2] recommended target AUC values of 5 and 7 mg ml^{-1} min for previously treated and previously untreated patients, respectively.

Although the relationship between the carboplatin AUC and toxicity is now well-defined, the carboplatin dose is nonetheless usually calculated using the patient's body surface area (BSA), which is not reliable measure for the GFR, particularly in patients who have previously received nephrotoxic medication. One practical reason why the present method is not yet widely employed is that the Calvert formula requires the GFR to be determined by an expensive, inconvenient, and invasive procedure (the [^{51}Cr]-EDTA method), which

cannot be carried out in every hospital. In addition, it requires the withdrawal of at least three to five blood samples at exact time points. Evidently, this is burdensome and costly for routine clinical use in most centers. It would be much more convenient to estimate the GFR using a simple creatinine clearance measurement or to calculate it on the basis of the serum creatinine concentration. It has been reported that the GFR as measured by the [^{51}Cr]-EDTA method correlates with the creatinine clearance ($r = 0.92$) [6, 11], and in many retrospective studies the method based on the latter has been used as an alternative for the [^{51}Cr]-EDTA method [9, 10, 13, 14]. However, it is clear that several factors, such as fluctuations in the endogenous creatinine production, imprecision of 24-h urine collections, and renal tubule abnormalities such as those caused by treatment with cisplatin, can cause erroneous estimates of the actual GFR.

Taking a different approach, Chatelut et al. [4] have recently proposed an alternative to calculate carboplatin clearance ($CL_{carbo-Ch}$). For their analysis, pharmacokinetic data obtained from 34 patients were analyzed using the nonlinear mixed-effect model (NONMEM), a population pharmacokinetics computer program. A two-compartment linear model was used, which included covariables such as age, gender, height, weight, BSA, serum protein levels, cisplatin pretreatment, and the serum creatinine concentration. The resulting formula was:

$$CL_{carbo-Ch}\ (ml/min) = 0.134 \times weight\ (kg) + \frac{218 \times weight\ (kg) \times [1.0.00457 \times age\ (years)]\ (\times 0.65\ if\ female)}{Serum\ creatinine\ (\mu M)}.$$

We investigated the accuracy and imprecision of carboplatin AUC predictions obtained using creatinine clearance or the Chatelut equation.

Patients and methods

Patient selection

This pharmacokinetics study was performed as part of a recently closed study in our institute, the clinical results of which will be reported elsewhere. In summary, all patients had histologically verified metastatic or unresectable non-small-cell cancer of the lung. Other eligibility criteria included a WHO performance status of ≤ 1, on age of ≤ 70 years, normal bone marrow function (WBC, $\geq 4.0 \times 10^9$/l; platelets, $\geq 100 \times 10^9$/l), a serum bilirubin level of $\leq 25\ \mu M$, a serum lactate dehydrogenase value of ≤ 250 U/ml, and creatinine clearance of ≥ 60 ml/min. All patients gave written informed consent.

Treatment plan

In this study, carboplatin was given in combination with etoposide, ifosfamide, and mesna (MICE regimen). Carboplatin at 350 mg/m^2 was given as a 1-h infusion on day 1, followed by ifosfamide infused over a 12-h period (1500 mg/m^2; days 1, 3, and 5) and etoposide given as a 1-h infusion (100 mg/m^2; days 1, 3, and 5). Co-administration of mercaptoethanesulfonate (mesna, 2.8 g/m^2) provided uroprotection.

Pharmacokinetics studies

Complete concentration-time curves were obtained from 14 patients. Serial samples were collected at 16 time points: immediately before and halfway through the infusion, at the end of the infusion, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 18, and 24 h after the end of the infusion. Plasma was obtained by immediate centrifugation (5 min at 1500 *g*; room temperature) of the samples. The plasma was transferred directly to an MPS-1 system with an YMT-30 membrane filter (Amicon Division, W.R. Grace & Co., Danvers, Mass., USA) and was centrifuged at room temperature for 10 min at 1500 *g*. The resulting plasma ultrafiltrate, representing the non-protein-bound active carboplatin fraction, was stored at -20°C until analysis. Carboplatin was quantitated using a validated method for platinum analysis based on Zeeman atomic absorption spectrometry [21]. The lower limit of quantitation (LLQ) of the assay was 0.1 μM, with the accuracy ranging from 93.9% (at the LLQ) to 103.3% and the within- and between-day precision varying from 1.5% to 10.2% (at the LLQ).

The exact AUC was calculated from the concentration-time curves by the trapezoidal method with extrapolation to infinity (C_{last}/λ_2, where C_{last} is the last measured concentration and λ_2 is the elimination rate constant). Linear regression analysis was performed on the initial and terminal phases of the linear-log concentration-time curve to obtain λ_1 and λ_2, respectively. Half-lives were calculated from the equations $t_{1/2\alpha} = 0.693/\lambda_1$ and $t_{1/2\beta} = 0.693/\lambda_2$. Other parameters were calculated using standard pharmacokinetic equations [8].

Calculation of clearance and statistical considerations

The creatinine clearance (CL_{cr}) was based on an accurate 24-h collection of urine and on the serum creatinine concentration (CL_{cr-24h}):

$$CL_{cr-24h}\ (ml/min) = \frac{Volume\ of\ urine\ after\ 24\,h\ (ml) \times creatinine\ concentration\ in\ urine\ (\mu M)}{Serum\ creatinine\ concentration\ (\mu M) \times 1440\ (min)}.$$

The serum creatinine concentration (expressed as micromolar) was measured on a CX5CE Synchron Clinical System instrument (Beckman Instruments, Inc., USA, 1990). The CL_{cr} was also calculated from the Cockcroft and Gauft equation (CL_{cr-CG} [5]:

$$CL_{cr-CG}\ (ml/min) = \frac{\{[140\text{-age(years)}] \times weight\ (kg)\}\ (\times 0.85\ if\ female)}{[0.813 \times serum\ creatinine\ concentration\ (\mu M)]}.$$

The expected carboplatin AUC values (expressed in milligrams per milliliter times minutes) were calculated by rearranging the Calvert formula into:

$$AUC(1) = Dose/(CL_{cr-24h} + 25) \quad (1)$$

and

$$AUC(2) = Dose/(CL_{cr-CG} + 25), \quad (2)$$

respectively. The carboplatin clearance was also calculated with the equation recently proposed by Chatelut et al. ($CL_{carbo-Ch}$) [4]:

$$CL_{carbo-Ch}\,(ml/min) = 0.134 \times weight\,(kg) + \frac{218 \times weight\,(kg) \times [1 - 0.00457 \times age\,(years)]\,(\times 0.65 \text{ if female})}{Serum\ creatinine\ (\mu M)}.$$

Here, the estimated AUC was obtained by:

$$AUC(3) = Dose/(CL_{carbo-Ch}). \quad (3)$$

The performance of the prediction of the AUCs was evaluated using the correlation coefficient (r), the relative mean prediction error (MPE%, a measure of bias) and its standard error (SE%), and the relative root mean-square prediction error (RMSE%, a measure of precision) [15]. These are:

$$MPE\% = \left[N^{-1} \sum_{i=1}^{N} (pe_i) \right] \times 100\%,$$

$$SE\% = \left\{ [N \times (N-1)]^{-1} \times \sum_{i=1}^{N} \left(pe_i\text{-}MPE \right)^2 \right\}^{1/2} \times 100\%, \text{ and}$$

$$RMSE\% = \left[N^{-1} \sum_{i=1}^{N} (pe_i)^2 \right]^{1/2} \times 100\%, \text{ respectively.}$$

where N is the number of AUC pairs (i.e., true with predicted values) and pe is the relative prediction error [$\ln(AUC_{true\ value})$-$\ln(AUC_{predicted})$]. The SE% values were used to calculate the 95% confidence intervals (95% CI).

Results

A total of 14 patients participated in this pharmacokinetics study. The average age was 52 (ranges, 32–67) years. Nine patients received carboplatin doses of 350 mg/m^2, whereas two patients had a dose reduction to 263 mg/m^2 (i.e., 75%) and three other patients received 175 mg/m^2 (i.e., 50%) because of severe thrombocytopenia in previous courses. The carboplatin concentration-time curves fitted well to a standard open two-compartment model with a mean initial half-life ($t_{1/2\alpha}$) of 65 (range 31–89) min and a mean terminal half-life ($t_{1/2\beta}$) of 4.3 (range, 1.5–7.2 h Table 1).

The mean observed AUC was 4.35 (range, 2.40–5.70) mg ml^{-1} min. The mean total carboplatin clearance was 132.8 (range 52.6–186.2) ml/min, and the mean volume of distribution was 50.7 (range, 18.9–84.7) l. The mean CL_{cr-24h} was 120.6 (range, 66–194) ml/min and the mean CL_{cr-CG} was 90.5 (range, 49.4–149.2) ml/min. It appeared that the AUCs could be estimated reasonably well using any of the equations (RMSE% values ranging from 13.8% to 17.4%, and r values ranging from 0.75 to 0.79; Table 2). However, Eqs. 1 and 2 were significantly biased in their prediction. The formula using CL_{cr-24h} (Eq. 1) systematically underestimated the AUC by about 10% (MPE, − 9.23%; 95% CI, − 2.1% to − 16.4%), whereas the formula using CL_{cr-CG} (Eq. 2) systematically overestimated the AUC by about 10% (MPE%, 10.9%; 95%, CI, 3.4–18.4%). In contrast, the formula using $CL_{carbo-Chatelut}$ (Eq. 3) was virtually unbiased (MPE% − 5.0%; 95% CI, from − 12.1% to 2.1%).

Table 1 Pharmacokinetic parameters of carboplatin (CL Total body clearance, $Vd\beta$ volume of distribution)

Dose (mg/m^2)	BSA (m^2)	AUC (mgml^{-1} min)	$t_{1/2\,\alpha}$ (min)	$t_{1/2\,\beta}$ (h)	CL (ml/min)	Vdβ (l)
175	1.7	2.40	41	3.1	116.7	31.7
175	1.5	3.60	83	5.2	52.6	23.8
175	1.7	3.72	64	3.4	114.9	33.7
263	1.9	4.08	70	3.9	111.3	37.8
263	1.9	4.68	67	4.3	104.7	66.2
350	1.9	4.10	61	4.4	165.7	62.6
350	1.8	4.28	72	3.8	147.3	48.6
350	1.7	4.43	89	7.2	136.6	84.7
350	2.0	4.51	81	7.0	155.1	93.6
350	2.5	4.62	67	4.3	177.4	66.2
350	2.1	4.81	31	1.5	145.6	18.9
350	1.5	4.86	62	4.5	122.9	47.5
350	2.0	5.10	56	3.7	186.2	59.7
350	2.1	5.70	65	3.9	122.8	34.4
Mean	1.9	4.35	65	4.3	132.8	50.7

Discussion and conclusions

Evidently, the current dosing of carboplatin based on the BSA is not optimal. The individual clearance of carboplatin differs among patients, causing a poorly predictable exposure (AUC) to the drug. A high AUC value correlates with more toxicity, whereas a low value is associated with decreased antitumor activity [7, 10, 12, 12, 20]. By means of the Calvert formula [Dose = target AUC × (GFR + 25)], one can adjust for the renal clearance (GFR) and achieve approximately equal drug exposure among patients. Although the usefulness of Calvert formula has been proven in several studies [7, 10, 12, 13, 20], its application in routine oncology practice remains very limited, probably because an inconvenient, invasive method is required to determine the GFR. Evidently, the formulas using the serum creatinine value described herein are more easily applied in clinical practice.

Although the values found for the pharmacokinetic parameters in this study (Table 1) are in good agreement with those reported in the literature [19], two of the formulas evaluated (Eqs. 1 and 2) were significantly biased in their prediction of the AUC. Thus, if patients are dosed on the basis of creatinine clearance as calculated by Eq. 1, some degree of overexposure to carboplatin will result. In contrast, if patients are dosed according to the calculated (Cockcroft-Gault) creatinine clearance as determined by Eq. 2, underexposure to carboplatin of about 10% will result. It is reasonable to assume that in retrospective studies in which the carboplatin AUC has been calculated from

Table 2 Estimated and measured clearance and AUC values (Creat serum creatinine concentration)

Gender	Age (years)	Weight (k)	Creat (μM)	CL_{cr-24h} (ml/min)	CL_{cr-CG} (ml/min)	AUC measured ($mgml^{-1}min$)	AUC(1) using CL_{cr-24h} ($mgml^{-1}min$)	AUC(2) using CL_{cr-CG} ($mgml^{-1}min$)	AUC(3) using $CL_{carbo-Chatelut}$ ($mgml^{-1}min$)
M	55	65.5	69	99	99	2.40	2.46	2.45	1.86
F	67	53.0	82	67	49	3.60	3.26	4.03	4.04
F	50	55.0	80	66	65	3.72	3.24	3.29	3.40
F	61	74.0	73	86	84	4.08	4.37	4.45	4.07
M	46	71.2	107	124	77	4.68	3.29	4.80	3.95
F	45	84.5	73	186	115	4.10	3.22	4.85	4.57
M	47	66.5	99	138	77	4.28	3.87	6.18	5.08
M	41	63.3	84	147	92	4.43	3.52	5.18	4.26
M	48	85.0	84	115	115	4.51	5.00	5.01	3.81
M	32	120.0	107	194	149	4.62	3.79	4.76	3.69
M	65	84.7	104	120	75	4.81	4.83	6.98	5.14
F	46	52.0	60	–	85	4.86	–	4.80	4.85
M	61	78.5	89	105	86	5.10	5.38	6.32	4.69
F	62	90.8	76	–	98	5.70	–	5.71	4.99
Mean	52	74.6	85	121	90	4.35	3.85	4.92	4.17
MPE%							− 9.23	10.9	− 5.03
RMSE%							15.42	17.35	13.76
r							0.75	0.79	0.79

the dose and the creatinine clearance, the AUC may have been either underestimated or overestimated, depending on which method has been used.

These findings are in accordance with the results obtained by Sørensen et al. [17], who have reported that the prospective use of CL_{cr-24h} may cause an overestimation of the GFR, resulting in overexposure. They analyzed data from 62 courses of carboplatin (250, 375, and 500 mg/m^2) given to 24 patients with ovarian cancer in combination with cyclophosphamide at 500 mg/m^2. The observed AUC values were compared with the predicted AUCs [AUC = Dose/(GFR + 25)], in which the GFR was estimated by CL_{cr-24h} and the [^{51}Cr]-EDTA method. It appeared that predictions based on the [^{51}Cr]-EDTA method were unbiased (MPE%, − 0.2%), in contrast to those based on CL_{cr-24h} (MPE%, − 13.1%). Furthermore, our findings are also in accordance with those of Calvert [1], who has reported that CL_{cr-CG} underpredicts the actual carboplatin clearance by about 12%. This was concluded from data obtained from 86 women with ovarian cancer [1]. Thus, when CL_{cr-CG} is used, AUC values will be lower than planned.

In contrast, a reliable estimation was obtained using Eq. 3 as proposed by Chatelut and co-workers [4]: no significant bias occurred. Furthermore, the error provoked by using this equation was comparable with the error found when using the original Calvert formula (RMSE%, ≈ 10% [3]). Thus, for both retrospective studies and future dosing strategies it can be concluded that this equation should be used to achieve the optimal carboplatin AUC. However, it must be noted that the co-administration of etoposide, ifosfamide, and mesna in our study might have influenced the pharmacokinetics of carboplatin. Therefore, before the [^{51}Cr]-EDTA method is widely substituted by one of the equations presented herein, prospective studies also examining other patient groups along with other dosages, agents, and renal functions must provide further assurance for this replacement.

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