Cancer Chemother Pharmacol (1998) 42: 307–312

ORIGINAL ARTICLE

Hiroaki Okamoto · Akira Nagatomo · Hideo Kunitoh
Hiroshi Kunikane · Koshiro Watanabe

Prediction of carboplatin clearance calculated by patient characteristics or 24-hour creatinine clearance: a comparison of the performance of three formulae

Received: 23 July 1997 / Accepted: 16 December 1997

Abstract *Purpose*: Carboplatin doses can be individualized using the formula of Calvert et al. (Calvert formula) dose (mg) = area under the plasma concentration versus time curve (AUC) · [glomerular filtration rate (GFR) + 25]. Creatinine clearance (Ccr), either measured by the 24-h method or calculated by the formula of Cockcroft and Gault [Cockcroft-Gault (CG) formula], is often substituted for the GFR. The CG formula is based on patient weight, age and sex, and the serum creatinine (Cr) concentration. Another method for predicting carboplatin clearance (CL) using patient characteristics has also been proposed by Chatelut et al. (Chatelut formula). This study was undertaken to evaluate the performance of the three formulae in predicting standard- and low-dose carboplatin pharmacokinetics. *Methods*: A total of 52 patients with advanced lung cancer were enrolled in this pharmacokinetic study; 37 received standard-dose carboplatin and 25 received low-dose carboplatin. The Cr concentration was measured using an enzymatic assay. The three formulae were used to predict carboplatin CL. The median absolute percent error (MAPE) for each formula was evaluated by comparing the calculated and observed CL. For comparison of AUCs, free platinum plasma concentrations were measured at intervals up to 24 h after carboplatin administration. AUCs were determined and compared with predicted values. *Results*: In the standard-dose carboplatin group, the MAPEs for the prediction of carboplatin CL from the 24-h Calvert, CG-Calvert and Chatelut formulae were 13%, 12% and 23%, respectively. In the low-dose carboplatin group, the corresponding MAPEs were 27%, 18% and 44%, respectively. Observed standard-dose carboplatin AUCs after aiming for target AUCs of 5 and 6 mg · min/ml using the Calvert formula based upon the 24-h Ccr were 5.3 ± 0.8 and 5.9 ± 0.8, respectively, indicating a small and acceptable bias compared with that predicted from the dosing formula. *Conclusions*: The pharmacokinetics of standard-dose carboplatin were accurately predicted by the Calvert formula based upon either 24-h or CG-calculated Ccr, but not by the Chatelut formula. Either CG-calculated or 24-h Ccr can be substituted for the GFR in the Calvert formula for the determination of individual doses. The poor predictability of the Chatelut formula found in this study might be the result of a differences in either the Cr assay or the patient population. Therefore, formulae which attempt to estimate GFR are not necessarily valid if either the Cr assay or the patient population is changed.

Key words Carboplatin clearance · AUC · Prediction · Calvert · Chatelut

Introduction

Carboplatin is an analog of cisplatin, which produces less nonhematological toxicity than cisplatin [2]. However, its dose-limiting toxicity is myelosuppression, particularly thrombocytopenia [7, 8]. The area under the plasma carboplatin concentration versus time curve (AUC) correlates well with the degree of myelosuppression and with the response rate [9, 19]. Carboplatin is a unique antineoplastic agent, for which the desired AUC can be controlled on the basis of individual renal function. The dosing of carboplatin can be individualized using the formula of Calvert et al. (Calvert formula): dose (mg) = AUC · [glomerular filtration rate (GFR) + 25] [3]. Creatinine (Cr) clearance (Ccr), either measured by the 24-h method or calculated by the formula of Cockroft and Gault [Cockcroft-Gault (CG)

This study was supported in part by Bristol-Myers Squibb, Tokyo, Japan, and was presented in part at the 32nd Annual Meeting of the American Society of Clinical Oncology, Philadelphia, Pa., 21 May 1996

H. Okamoto (✉) · A. Nagatomo · H. Kunitoh
H. Kunikane · K. Watanabe
Division of Respiratory Medicine,
Yokohama Municipal Citizen's Hospital, 56 Okazawa-cho,
Hodogaya-ku, Yokohama-city, Kanagawa 240, Japan
Tel. +81-4-5331-1961; Fax +81-4-5332-5599

formula] [6], is often substituted for the GFR in clinical practice and in clinical trials [1, 10, 12, 23] because the measurement of GFR ([^{51}Cr]-EDTA method) is an expensive, inconvenient and invasive procedure. Chatelut et al. have recently proposed a formula to estimate carboplatin clearance (CL) using the serum Cr concentration and patient characteristics including sex, weight and age (Chatelut formula) [5].

An accurate method for carboplatin dose determination that does not require the use of a radioactive isotope or a 24-h urine collection would be very useful in clinical practice. Therefore, this study was undertaken to evaluate the performance of the three formulae (the Calvert formula based upon 24-h Ccr, the Calvert formula based upon CG-calculated Ccr, and the Chatelut formula) in predicting standard- and low-dose carboplatin pharmacokinetics. Predictive AUC values derived from the Calvert formula based upon 24-h Ccr were also compared with observed AUC values.

Patients and methods

Patient selection and treatment plans

A group of 52 patients on whom complete pharmacokinetic studies had been performed during recent phase II studies at our institution participated in this study. The clinical results are reported elsewhere [11, 17, 24]. In summary, 25 patients with locally advanced non-small-cell lung cancer received low-dose carboplatin (25 mg/m^2, i.v.) daily as a radiosensitizer, with twice-daily thoracic radiotherapy (1.5 Gy each time, 6 h apart) to a total of 60 Gy in 40 fractions over 4 weeks. A further 20 patients with small-cell lung cancer received standard-dose carboplatin with a target AUC of 5 mg · min/ml i.v. on day 1, plus etoposide 100 mg/m^2 i.v. on days 1 to 3. Finally, 7 patients with metastatic non-small-cell or recurrent small-cell lung cancer received standard-dose carboplatin with a target AUC of 5 or 6 mg · min/ml i.v. on day 1, plus irinotecan (CPT-11) 60 mg/m^2 i.v. on days 1, 8 and 15. The durations of carboplatin infusion in the standard- and low-dose protocols were 60 and 15 min, respectively. The common eligibility criteria included an ECOG performance status of ≤2, normal bone marrow function (WBC ≥4000/mm^3, platelet ≥10×10^4/mm^3), a serum bilirubin level of ≤2.0 mg/dl and a transaminase level not more than twice normal. All patients gave written informed consent.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed on chemotherapy day 1. Blood samples were collected into heparinized tubes at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after administration of standard-dose carboplatin over 60 min or 0, 0.5, 1, 2, 4 and 24 h after administration of low-dose carboplatin over 15 min. The times of blood sample collections were from the end of the infusion. Plasma ultrafiltrates were prepared immediately. The free platinum plasma concentration was measured using flameless atomic absorption spectrophotometry, as described previously [14]. The lower limit of sensitivity of the assay for free platinum was 10 ng/ml. The postinfusional plasma concentration versus time data were fitted to monoexponential equations [16, 18] to calculate the last elimination rate constant by the least squares method (linear regression) using log-transformed concentrations and time. The AUC for free platinum was obtained using standard equations [15, 16]. We used the trapezoidal method and extrapolation of the last elimination phase for the calculation of AUC.

Definition of carboplatin clearance

The Calvert formula is: dose (mg) = AUC · (GFR + 25). Carboplatin CL is calculated by the equation: dose/AUC = GFR + 25. In our study, either the 24-h Ccr or the CG-calculated Ccr was substituted for the GFR, and the Cr concentration was measured using an enzymatic assay (AUTO L"MIZUHO" CRE kit, Mizuho Medy Co., Japan). In the Calvert formula based upon 24-h Ccr, the predicted carboplatin CL was calculated using the formula with GFR replaced by 24-h Ccr. The Ccr was also calculated from the CG formula [6]: Ccr = {[140 − age(years)] · weight (kg)}(× 0.85 if female)/72 · [serum Cr (mg/dl)]. The predicted carboplatin CL was also calculated using the Calvert formula with GFR replaced by CG-calculated Ccr. The predicted carboplatin CL was also calculated using the Chatelut formula: 0.134 · weight (kg) + 2.46 · [weight (kg)/serum Cr (mg/dl)] · [1 − 0.00457 · age (years)] · (× 0.686 if female). Although a micromolar concentration of Cr was used in the original Chatelut formula, the value is expressed in milligrams per decilitre in our study, and the formula was modified appropriately.

Calculation of the predictive performance of the three formulae

The performance of each formula in predicting carboplatin CL was assessed by calculating the percent error as follows: [(calculated CL − observed CL)/observed CL] · 100. The absolute percent error was calculated as follows: (|calculated CL − observed CL|/observed CL) · 100, where the observed CL was the CL obtained from the pharmacokinetic analysis and the calculated CL was the value obtained from the formula using either morphological patient characteristics or the value Ccr + 25 [5]. In addition, a paired *t*-test was used to analyze the differences between the predicted and observed carboplatin CL.

Results

Of the 52 patients in this pharmacokinetic study, 25 received low-dose and 27 standard-dose carboplatin. The median age was 71 (range 46–87) years and the median body weight was 53 (range 33–95) kg. There were 7 females and 45 males. Of the 7 females, 4 received standard-dose carboplatin (3 with etoposide and 1 with CPT-11) and 3 received low-dose carboplatin daily as a radiosensitizer. The median serum Cr concentration was 0.81 (range 0.43–1.91) mg/dl and the median 24-h Ccr was 78 (range 20–145) ml/min.

Figures 1 and 2 show the relationship between the observed carboplatin CL and the CL values predicted on the basis of the three formulae for low- and standard-dose carboplatin. The median percent error (MPE) and the median absolute percent error (MAPE) are shown in Tables 1 and 2. The low-dose carboplatin CL calculated according to all three formulae correlated poorly with the observed CL. The best predictor for low-dose carboplatin CL was the Calvert formula based upon CG-calculated Ccr. In contrast, standard-dose carboplatin CL calculated according to the three formulae correlated more closely with the observed CL. The standard-dose carboplatin CL was accurately predicted by Calvert formula based upon both 24-h and CG-calculated Ccr, and the precision of these two formulae was almost identical. However, both standard- and low-dose

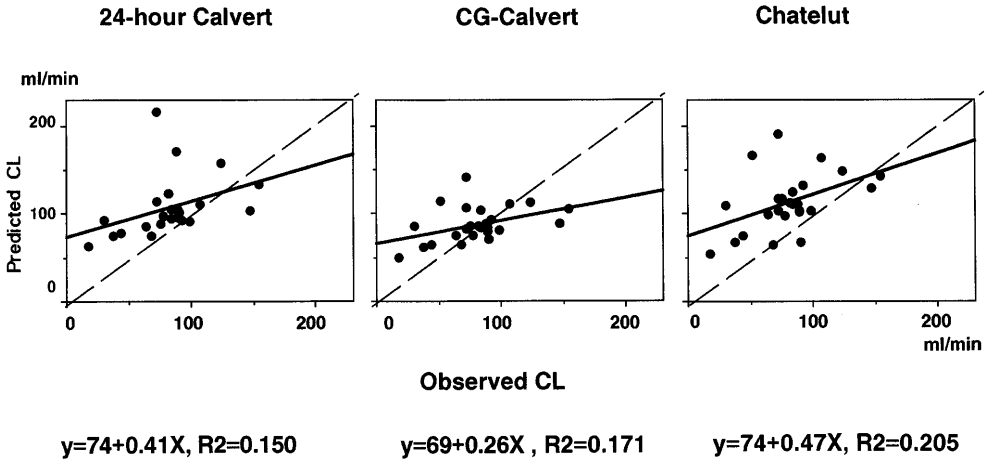

Fig. 1 Relationship between observed carboplatin clearances and the clearances predicted on the basis of the three formulae for low-dose carboplatin (25 mg/m^2). The line of identity (- - - -) and the linear regression line (——) are shown

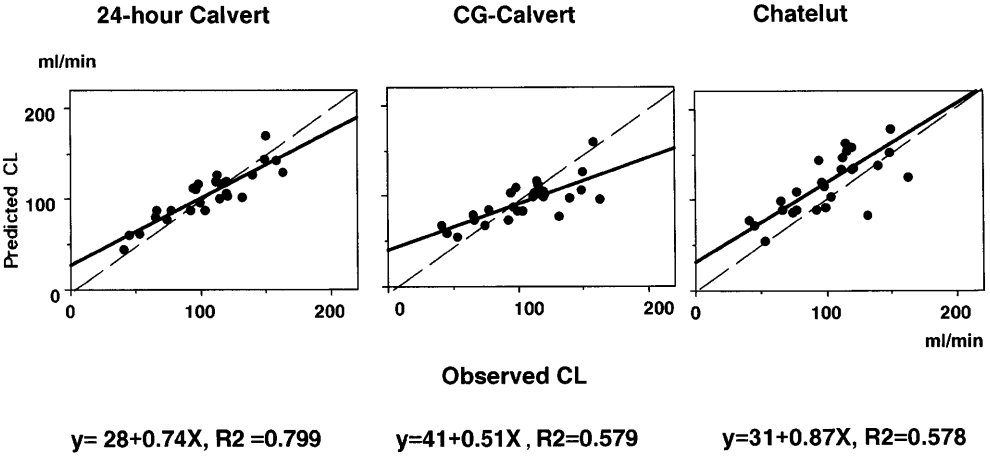

Fig. 2 Relationship between observed carboplatin clearances and the clearances predicted on the basis of the three formulae for standard-dose carboplatin. The line of identity (- - - -) and the linear regression line (——) are shown

Table 1 Performance of the three formulae for predicting low-dose carboplatin clearance (*CL* clearance, *MAPE* median absolute percent error, *MPE* median percent error). Values are the median (range) of the results obtained from 25 patients

	Measured CL	24-h Calvert	CG-Calvert Predicted CL	Chatelut
	82 (17 to 155)	98 (63 to 217)	85 (50 to 142)	111 (54 to 190)
P-value[a]		0.007	0.244	0.001
MAPE[b]		27 (0 to 263)	18 (0 to 187)	44 (4 to 265)
MPE[c]		27 (−29 to 99)	1 (−32 to 187)	44 (−25 to 265)

[a] Paired *t*-test, predicted vs measured carboplatin CL
[b] Absolute percent error = (|calculated CL − observed CL|/observed CL) × 100
[c] Percent error = [(calculated CL − observed CL)/observed CL] × 100

carboplatin CL were poorly predicted by the Chatelut formula. Figure 3 shows the observed standard-dose carboplatin AUCs after aiming for target AUCs of 5 and 6 mg · min/ml, for which doses were calculated using the Calvert formula based upon 24-h Ccr. The respective AUC values were 5.3 ± 0.8 and 5.9 ± 0.8 mg · min/ml, indicating a small and acceptable bias compared with values predicted from the dosing formula.

Discussion

Calvert et al. have reported that AUC-based dosing of carboplatin results in more acceptable toxicity and greater efficacy against carboplatin-sensitive tumors than dosing strategies based on BSA (body surface area) [4]. Although dose adjustment based on isotopic determination of GFR has been proposed, it has not been widely applied because of the inconvenience,

Table 2 Performance of the three formulae for predicting standard-dose carboplatin clearance (*CL* clearance, *MAPE* median absolute percent error, *MPE* median percent error). Values are the median (range) of the results obtained from 27 patients

	Measured CL	24-h Calvert	CG-Calvert Predicted CL	Chatelut
	104 (41 to 163)	103 (45 to 170)	96 (54 to 160)	119 (54 to 230)
P-value[a]		0.814	0.024	0.001
MAPE[b]		13 (0 to 33)	12 (1 to 66)	23 (0 to 88)
MPE[c]		6 (−22 to 33)	−8 (−41 to 66)	19 (−37 to 88)

[a] Paired *t*-test, predicted vs measured carboplatin CL
[b] Absolute percent error = (|calculated CL − observed CL|/observed CL) × 100
[c] Percent error = [(calculated CL − observed CL)/observed CL] × 100

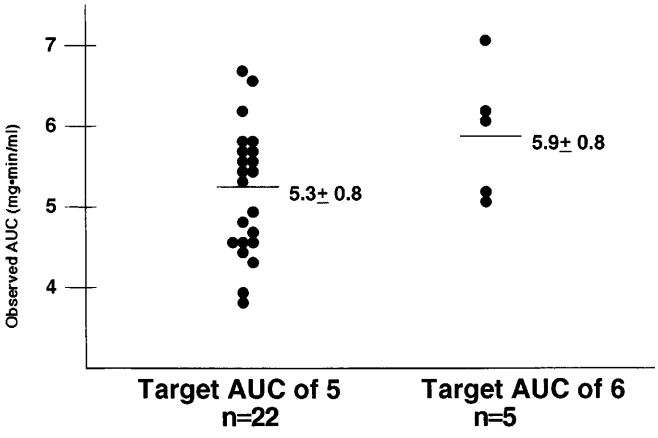

Fig. 3 Observed standard-dose carboplatin AUCs in relation to target AUCs of 5 ($n = 22$) and 6 ($n = 5$) mg · min/ml, following dosing using the Calvert formula based upon 24-h Ccr

invasiveness and expense of determining the GFR. Therefore, either 24-h Ccr or CG-calculated Ccr has often been substituted for the GFR in clinical practice and in clinical trials [1, 10, 12, 23]. However, there is some evidence that carboplatin AUC is biased when 24-h Ccr or CG-calculated Ccr is substituted for the GFR in the Calvert formula. Several investigators have reported that the use of 24-h Ccr leads to an overestimation of the GFR, resulting in overexposure [1, 21, 23]. Others have reported that the use of 24-h Ccr leads to an underestimation of the GFR, resulting in an AUC about 10–15% lower than the ideal [10]. Similarly, dosing of patients according to the CG-calculated Ccr as determined by the Calvert formula results in underexposure to carboplatin by about 10% or more [12, 13]. Recently, Chatelut et al. have found that age, weight, sex, and plasma Cr are significant independent variables in determining carboplatin CL using the nonlinear mixed-effect model (NONMEM), a population pharmacokinetics computer program [5]. They have devised a formula based upon these parameters for use in carboplatin dose determination. Furthermore, they emphasized that this method of prediction is as accurate as methods based on the measurement of GFR.

It is interesting to note that carboplatin CL was very poorly predicted by the Chatelut formula for both low- and standard-dose carboplatin in our study. As shown in Tables 1 and 2, predicted carboplatin CL values determined by the Chatelut formula were higher than measured carboplatin CL values. Dosing according to the Chatelut formula will result in overexposure to carboplatin. In contrast, for standard-dose carboplatin, predictions of carboplatin CL according to the Calvert formula based on 24-h or CG-calculated Ccr were almost identical, and more accurate than values calculated by the Chatelut formula. The MAPE and MPE for the predictions from the Calvert formula based on 24-h or CG-calculated Ccr were comparable with those originally obtained by Chatelut et al. [5]. Furthermore, actual standard-dose carboplatin AUCs observed after using the Calvert formula based upon 24-h Ccr to calculate the dose indicated a small and acceptable bias compared with the values predicted from the dosing formula.

These results are quite different from those of others which have demonstrated that the best prediction of carboplatin CL is obtained using the Chatelut formula, and not those based upon 24-h Ccr or CG-calculated Ccr [1, 10, 12, 13, 23]. Although the reason for our results being different from those of others remains unclear, it could be a consequence of methodological differences in the measurement of Cr between different laboratories. The data used to derive the CG formula were based on the alkaline picrate method, and variations of this method have been used by most United States and European investigators. It is well known that the alkaline picrate method often overestimates the plasma Cr level owing to interfering chromogens. In our hospital, the Cr level is measured using an enzymatic assay, which is a more accurate method for the measurement of Cr. It is possible that this methodological difference influenced the predictions of carboplatin CL. Another possibility may be a drug–drug interaction with the coadministered of etoposide or CPT-11, which might influence the pharmacokinetics of carboplatin. Indeed, the pharmacokinetics of low-dose carboplatin administered as a single agent were poorly predicted by all three formulae.

A further possibility may be differences in patient characteristics between our study and the original study by Chatelut et al. Japanese people are usually smaller and lighter than American or European people. The

median body weight of the patients in our study was 53 kg; in the study by Chatelut it was 70 kg. In addition, the proportion of men included in our study was high (87%) compared with the study by Chatelut et al. [5]. The Cr level is dependent on both renal elimination and skeletal muscle production [5]. Muscle mass correlates positively with weight and negatively with age, and is larger in men than in women. The subjects in our study were mostly elderly and the median age was 71 years. It has been reported that elderly patients have a reduced capacity for non-renal clearance of carboplatin, resulting in overexposure [22]. Furthermore, there was a very wide range of renal functions (20 to 145 ml/min) in our study, but a narrower range of renal functions in the study by Chatelut et al. Thus, patient characteristics differing from those in other studies may explain the poor predictive performance of the Chatelut formula in our study. Therefore, it may be that the Chatelut formula should not be used for a patient population differing from that used in the original study by Chatelut et al.

This is the first study of low-dose carboplatin CL in relation to the Calvert formula. As shown in Fig. 1, the points were widely scattered, suggesting that the low-dose carboplatin CLs calculated using all three formulae correlated poorly with the observed CL. Although the reason for this poor prediction remains unclear, it may be that the pharmacokinetics of low-dose carboplatin CL cannot be fitted to the Calvert formula. One reason for the poor predictability may be because of tubular reabsorption [20]. Sorensen et al. have shown that carboplatin CL is about 5% lower than GFR because of tubular reabsorption. With low-dose carboplatin, this mechanism may be much more significant. Another reason may be a difference in the rate of infusion between the two groups. The rate of infusion in the low-dose group was slower than in the standard-dose group, and it might be that the rate of tissue binding is related to the infusion rate, making renal elimination less relevant. A further reason for the poor correlation may be because of the BSA-based dosing strategy in the low-dose cohort. The standard-dose carboplatin CL was more accurately predicted than the low-dose carboplatin CL, especially by formulae based upon the 24-h Ccr and CG-calculated Ccr.

Observed standard-dose carboplatin AUCs, after aiming for target AUCs of 5 and 6 mg · min/ml using the Calvert formula based upon 24-h Ccr, were comparable with the target AUCs, but a small and acceptable bias was observed (Fig. 3). One reason for the bias may be the fact that 24-h Ccr did not always accurately reflect the true GFR in some patients.

In summary, the pharmacokinetics of standard-dose carboplatin were most accurately predicted by the Calvert formula based upon either CG-calculated or 24-h Ccr. Therefore, both CG-calculated and 24-h Ccr can be substituted for the GFR in the Calvert formula for determination of individual doses. The poor predictability of the Chatelut formula in our study suggests that formulae which attempt to estimate GFR are not necessarily valid if the Cr assay or the patient population is changed.

Acknowledgements We acknowledge the review and criticism by Dr. A. Hilary Calvert, University of Newcastle, UK, and Dr. Luigi Lenaz, Bristol-Myers Squibb.

References

1. Ando Y, Minami H, Ando M, Sakai S, Saka H, Shimokata K (1996) Risk of carboplatin overdosing when creatinine clearance is used in the Calvert formula (abstract). Proc Am Soc Clin Oncol 15: 179
2. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR (1982) Early clinical studies with cis-diammine-1,1-cyclobutanedicarboxylate platinum II. Cancer Chemother Pharmacol 9: 140
3. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7: 1748
4. Calvert AH, Boddy A, Bailey NP, Siddiqui N, Humphreys A, Hughes A, Robson L, Gumbrell L, Thomas H, Chapman F, Proctor M, Simmons D, Oakey A, Lind MJ, Sinha DV, Newell DR (1995) Carboplatin in combination with paclitaxel in advanced ovarian cancer: dose determination and pharmacokinetic and pharmacodynamic interactions. Semin Oncol 22 [Suppl 12]: 91
5. Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roche H, Houin G, Bugat R (1995) Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87: 573
6. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16: 31
7. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thomson BW, Aisner J (1984) Pharmacokinetics and dosage reduction of cis-diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. Cancer Res 44: 5432
8. Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J (1985) Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum(II) analogue diamminecyclobutanedicarboxylatoplatinum. Cancer Res 45: 6502
9. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S, Wiltshaw E (1992) Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10: 520
10. Kearns CM, Belani CP, Erkmen K, Zuhowski M, Hiponia D, Zacharski D, Engstrom C, Ramanathan R, Trenn MR, Aisner J, Egorin MJ (1995) Pharmacokinetics of paclitaxel and carboplatin in combination. Semin Oncol 22 [Suppl 12]: 1
11. Kunitoh H, Watanabe K, Nagatomo A, Okamoto H, Kimbara K (1997) Concurrent daily carboplatin and accelerated thoracic radiotherapy in locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 37: 103
12. Langer CJ, Leighton JC, Comis RL, O'Dwyer PJ, McAleer CA, Bonjo CA, Engstrom PE, Litwin S, Ozols RF (1995) Paclitaxel and carboplatin in combination in the treatment of advanced non-small-cell lung cancer: a phase II toxicity, response, and survival analysis. J Clin Oncol 13: 1860
13. Laurence JCW, Sjoerd R, Wim WBH, Robert AAM, Jos HB (1996) Evaluation of formulas using the serum creatinine level to calculate the optimal dosage of carboplatin. Cancer Chemother Pharmacol 37: 266

14. LeRoy AF, Wehling ML, Sponseller HL, Friauf WS, Solomon RE, Dedrick RL (1977) Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med 18: 184
15. Loo JCK, Riegelman S (1970) Assessment of pharmacokinetics constants from postinfusion blood curves obtained after i.v. infusion. J Pharm Sci 59: 53
16. Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH (1989) Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. Cancer Chemother Pharmacol 23: 367
17. Okamoto H, Nagatomo A, Kunitoh H, Watanabe K (1995) A combination phase I-II study of carboplatin/irinotecan plus G-CSF with the Calvert equation in patients with advanced non-small cell lung cancer (NSCLC) (abstract). Proc Am Soc Clin Oncol 14: 373
18. Ottaway JH (1973) Normalization in the fitting of data by iterative methods: application to tracer kinetics and enzyme kinetics. Biochem J 134: 729
19. Sorensen BT, Stromgren A, Jakobsen P, Jakobsen A (1991) Dose toxicity relationship of carboplatin in combination with cyclophosphamide in ovarian cancer patients. Cancer Chemother Pharmacol 28: 397
20. Sorensen BT, Stromgren A, Jakobsen P, Nielsen JT, Andersen LS, Jakobsen A (1992) Renal handling of carboplatin. Cancer Chemother Pharmacol 30: 317
21. Sorensen BT, Stromgren A, Jakobsen P, Jakobsen A (1993) Is creatinine clearance a sufficient measure for GFR in carboplatin dose calculation? (abstract). Eur J Cancer 29: s110
22. Vijgh WJF van der (1991) Clinical pharmacokinetics of carboplatin. Clin Pharmacokinet 21: 242
23. Wada T, Nakamura T, Maeda Y, Maruyama H, Onishi Y, Hatae M (1996) Actual carboplatin AUC had better correlation with Chatelut's formula than arranged Calvert's formula using 24-hr creatinine clearance (abstract). Proc Am Soc Clin Oncol 15: 475
24. Watanabe K, Okamoto H, Nagatomo A, Kunitoh H (1995) Carboplatin (CBDCA) combined with etoposide (VP) in the treatment of poor-risk small cell lung cancer (SCLC): a phase II study based on a pharmacokinetically guided dose schedule (abstract). Proc Am Soc Clin Oncol 14: 372