ANTICANCER RESEARCH *34*: 465-470 (2014)

Review

Standardization of Chemotherapy and Individual Dosing of Platinum Compounds

FLORENT PUISSET[1], ANTONIN SCHMITT[2] and ETIENNE CHATELUT[1]

[1]*Institut Claudius-Regaud and EA4553, University of Toulouse, Toulouse, France;*
[2]*Centre Georges-François Leclerc and EA4184, University of Bourgogne, Dijon, France*

Abstract. *Platinum compounds represent a pharmacological class essential for the treatment of certain types of cancer. Cisplatin, carboplatin, and oxaliplatin, share some physiochemical and pharmacological properties, in particular the ability to form DNA adducts. Carboplatin may be considered as an analog of cisplatin, but its pharmacokinetic properties, side-effects, and intrinsic activity are significantly different from those of cisplatin. The choice of one of these two compounds may be made rationally based on the individual patient's characteristics.*

The concept of individual dosing (*i.e.* not giving the same dose to every patient) is based on the objective of giving a dose adapted to the individual pharmacokinetic parameters of each patient in order to minimize the difference between patients in terms of systemic drug concentrations.

In oncology, numerous studies have shown that the relevant plasma concentration in terms of pharmacokinetic-pharmacodynamic (PK-PD) relationships of cytotoxic drugs is the area under the curve of plasma concentrations *versus* time (AUC). The AUC of a patient is dependent on the administered dose, and their drug clearance (CL) if the drug is given intravenously (*i.v.*) (or apparent oral CL, CL/F, if the drug is given through extravascular route) where AUC=Dose/CL (or AUC=F.Dose/CL with F for bioavailability coefficient).

This principle has been used by Pinkel (1) and Frierich *et al.* (2) to extrapolate cytotoxic doses from toxicological animal studies to human phase 1 trials by using body surface area (BSA). By comparing effective dosages of several cytotoxics among mammals, the doses differed less between species when based on BSA (mg/m^2) than when expressed by body weight (BW) (mg/kg), and, of course, when expressed in milligrams. Calculation of the individual dose according to BSA has been generalized in oncological practice by making the hypothesis that the capacity of elimination of a drug is proportional to the patient's morphology. However, several PK studies have shown that the correlation between BSA (usually calculated according to the Dubois formula based on both BW and height) and drug clearance observed in patients with cancer is generally weak.

In the present article, we consider the benefit, and limit of dosing by BSA for platinum compounds. Conclusions will be very different with BSA dosing that may be recommended (although simplified according to the dose-banding concept) for cisplatin, hence BSA dosing has been substituted by AUC dosing methods for carboplatin. The contradictory strategies for these two platinum analogs are justified by their different PK. Since they are injected into the blood, both cisplatin and carboplatin are hydrolyzed spontaneously (non-enzymatic biotransformation) into di-aquaplatin, which represents their common active metabolite (Figure 1). This reactive di-aquaplatin may form covalent bonds not only with DNA (platinum adducts), but also with proteins, and particularly plasma proteins. However, carboplatin is more stable than cisplatin. Cisplatin is therefore hydrolyzed more quickly and at a higher proportion in plasma. As a consequence, this non-reversible plasma protein binding represents the major route of elimination of the active metabolite of cisplatin, then carboplatin is mainly eliminated through the kidneys. The percentage of platinum excreted in the urine during the first 24 hours post-infusion is around 30% for cisplatin *versus* around 70% for carboplatin. Moreover, in the kidney, both tubular absorption and secretion have been described for cisplatin, thus glomerular filtration represents the main process of elimination for carboplatin. Cisplatin, but not carboplatin, is a substrate of organic cationic transporter 2 (OCT2) expressed in the basolateral membrane of proximal tubular cells responsible for the tubular re-absorption of cisplatin (3). This explains

Correspondence to: Professor Etienne Chatelut, Institut Claudius-Regaud and EA4553, University of Toulouse, France. E-mail: chatelut.etienne@claudiusregaud.fr

Key Words: Platinum, chemotherapy, dosing, review.

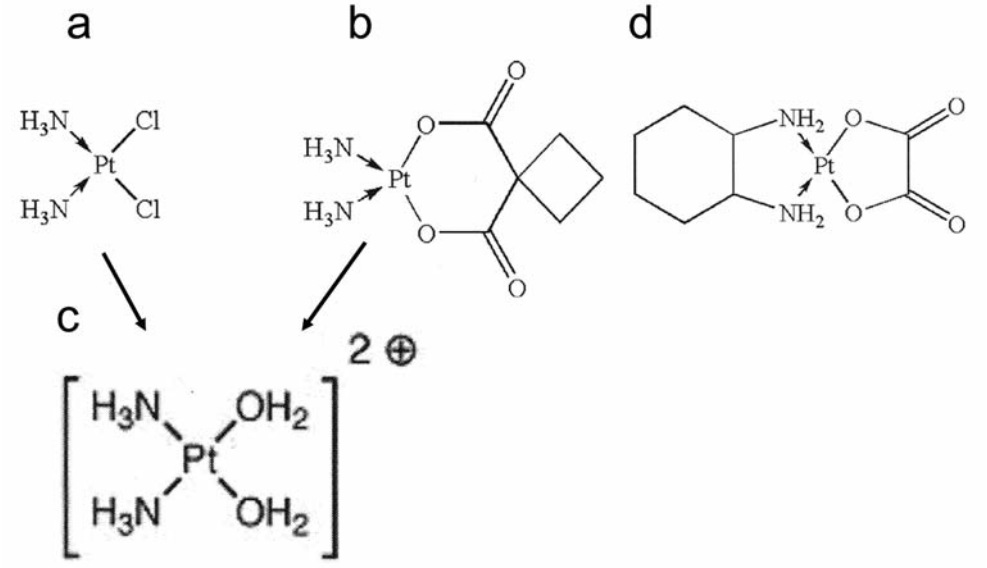

Figure 1. *Chemical strucutre of cisplatin (a), carboplatin (b) and their active metabolite diaquaplatin (c); and oxaliplatin (d).*

the higher nephrotoxicity of cisplatin in comparison with carboplatin. The PK consequence is that carboplatin clearance is highly dependent on the patient's glomerular filtration rate (GFR) in contrast to cisplatin. However, the patient's GFR should be monitored before and after cisplatin treatment as a marker of cisplatin toxicity.

Individual Dosing of Carboplatin

According to the most current administration schedule (*i.e.* one hour *iv* infusion), ultrafiltrable plasma levels of carboplatin decrease bi-exponentially after the end of infusion. In the ultrafiltrate, carboplatin half-lives of distribution and elimination are 23 and 120 min, respectively. A terminal half-life of about six days is described: it corresponds to the elimination of the bound drug form. The total elimination clearance of plasma ultrafiltrate is on average 107 ml/min (81 ml/min due to the renal clearance and 26 ml/min due to non-renal clearance) (4). Finally, in a patient with normal renal function, approximately 80% of the dose administered is recovered in the urine after 24 h (5).

Because carboplatin elimination is mainly mediated by the kidneys and due to heterogeneity in renal function, carboplatin CL shows an important inter-individual variability (6). Age or weight may explain part of this variability, however, other factors such as compressive pelvic tumor (bladder cancer, gynecological tumor) indicated for carboplatin may also interfere. Moreover, carboplatin is frequently prescribed as an alternative to cisplatin for patients with renal failure for whom cisplatin is contra-indicated (7). This important variability explains why the relationship between AUC and hematotoxicity is tighter than that with dose. The AUC represents the patient's carboplatin exposure. It is, however, much more difficult to determine the relationship between exposure and efficacy. First of all, because several weeks are needed to demonstrate a therapeutic benefit, but also because additional factors, such as resistance development, have a higher impact than PK.

The carboplatin exposure-toxicity relationship justifies the use of the following equation to calculate the dose to be given: dose=CL. AUC. To be used, one needs on one hand to predict individual carboplatin CL and on the other hand to select a target AUC. Many studies have focused on the prediction of carboplatin clearance (*via* formulae), including those from Egorin, Calvert, Chatelut and Thomas (6, 8-13).

The aim of these formulae is to reduce the PK variability by taking into account relevant patient characteristics. They allow the carboplatin dose to be individualized prior to any PK investigation. As carboplatin is mainly eliminated by renal glomerular filtration, Egorin *et al*. developed a formula based on creatinine clearance measurement (requiring 24-hour urine collection) (6). Some years later, Calvert *et al*. proposed a formula based on the measurement of GFR by an isotopic method, which represents carboplatin renal clearance, which is added to 25 ml/min (non-renal clearance of carboplatin) (13). Due to the complexity of implementation of the isotopic measurement of GFR, the Calvert formula is now used with Cockcroft-Gault formula to predict GFR. In 1995, Chatelut *et al*. proposed a formula

based on the same patient characteristics as for the Calvert/Cockcroft-Gault formula (that is to say, age, weight, sex and creatinine), but which allows direct prediction of carboplatin CL, without estimating the GFR (9). This formula has been modified to take overweight into account, for which the actual weight is replaced by the arithmetic mean of the actual weight and ideal weight (8), but also takes into account the bias due to different serum creatinine measurement methods by the use of a correction factor (14).

Nevertheless, because all these formulae are based on creatinine to reflect GFR, they are all subject to the biases inherent in its use. While creatinine is dependent on GFR, it is also dependent on muscle mass, resulting in an overestimation of the clearance in obese or underweight patients. In 2005, Thomas *et al*. suggested the use of cystatin C (for review refer to Newman *et al*. (15)), a new marker of glomerular filtration, in addition to other features to predict carboplatin clearance (12). The authors demonstrated that cystatin C alone did not perform better than creatinine, but that the use of both GFR markers in addition to the three other usual covariates brings a significant improvement in clearance estimation compared to formulae based on only four covariates. The Thomas formula was validated (and slightly modified) by Schmitt *et al*. (11). In this last article, the authors showed that the bias and imprecision between observed and predicted clearance were lower with the modified Thomas formula compared to the Calvert/Cockcroft-Gault formula. If this is true for normal-weight patients, it is more interesting that it is also true for obese or underweight patients.

In contrast to studies dealing with clearance, very few studies exist on the AUC to be administered in order to achieve an optimal exposure, that is to say, a carboplatin AUC that generates a manageable toxicity, while optimizing the likelihood of response. AUC was mainly empirically determined depending on concomitant chemotherapies and previous treatments (16-18). The dose-limiting toxicity of carboplatin is myelosuppression, in particular thrombocytopenia. In 2010, Schmitt *et al*. developed PK/PD models that describe neutropenia and thrombocytopenia due to carboplatin (19). The interest of this methodology is to consider the entire time course of platelet or absolute neutrophil counts and not only the likelihood of specific grades of toxicity based on observed nadirs. Moreover, such an approach allows for the use of patient characteristics to explain PD variability. The results of this study indicate that if associated chemotherapies explain the major part of the variability in hematopoietic sensitivity, none of the demographic, biologic or pharmacogenetic covariates have a significant impact. According to this article, thrombocytopenia represents the dose-limiting toxicity in patients receiving either carboplatin in monochemotherapy or in combination with gemcitabine, and neutropenia for patient treated in association with paclitaxel. More precisely, patients receiving carboplatin in association with any other chemotherapeutic drug experience neutropenic sensitivity 76% greater than when treated in monotherapy. Meanwhile, patients co-treated with paclitaxel, VP16 or gemcitabine have 24% lower or 45% and 133% greater thrombopenic sensitivity, respectively, compared to other patients (Figure 2).

Dose Banding of Cisplatin

Cisplatin (cis-diammine dichloroplatinum) is a widely used cytotoxic agent which remains a reference drug in a broad spectrum of malignancies such as those of testis, lung, ovary, germ cell, bladder, head and neck, cervical and endometrial cancer.

Cisplatin, like carboplatin is also irreversibly bound to plasma proteins; unbound cisplatin is mainly eliminated by the kidneys, but plasma protein binding is a major route of elimination of cisplatin (20).

A significant correlation between AUC and DNA-adduct formation in white blood cells, and the significantly higher AUC in responders than in non responders, support the hypothesis that the variability in dose-response is mainly supported by PK variability (21). The calculation of cisplatin dose is usually adjusted by an individual's BSA. This use is supported by a significant correlation between BSA and CL of free cisplatin (CL_{free}) (22). A significant difference in CL_{free} has been shown between patients with BSA under 1.7 m^2 (49.7 l/h) and those with BSA above 2.0 m^2 (65.4 l/h) (23). By a population PK approach in 285 patients with normal renal function, de Jong *et al*. observed, that BSA was the only significant covariate that could explain variability of both CL_{free} and V (24). The influence of BSA on CL_{free} variability was also observed in patients with extreme morphological characteristics. CL_{free} in obese patients (*i.e*. with body-mass index greater than 30 kg/m^2) seems significantly higher than CL_{free} in lean patients (60.0 l/h *vs*. 53.3 l/h respectively, p=0.007) (25).

Urien *et al*., observed that serum creatinine was another significant covariate that could explain in part CL_{free} variability (22); they concluded that patients with renal impairment should be given a lower dosage than patients with normal renal function. Since the contribution of renal elimination is a minor route of elimination, renal function is not used for individual dosing but for assessing the nephrotoxicity of cisplatin.

Even if BSA seems the only validated tool for individual dosing of cisplatin, BSA explains only a small part of the variability in CL_{free}: when corrected for BSA, the interindividual variability remained of the same order (from 25.6 to 23.6%) (23). Thus, BSA although relevant, is not an accurate tool for individual dosing, so various alternate dosing strategies have been proposed.

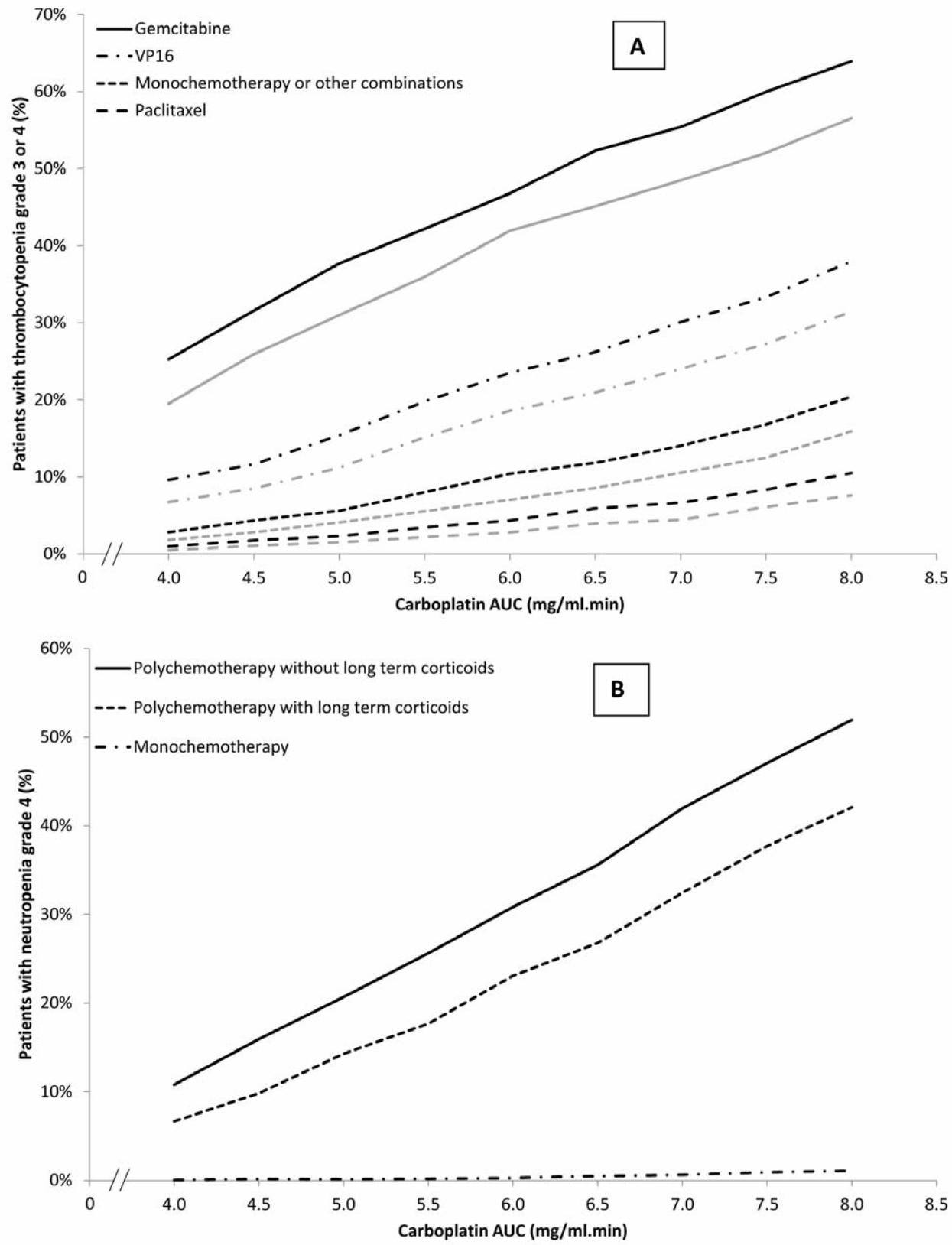

Figure 2. *Percentage of patients experiencing hematotoxicity according to carboplatin AUC, depending on the combined drug with carboplatin (19). A. Thrombocytopenia grade 3 or 4 (Black: patient with previous chemotherapy; gray: no previous chemotherapy); B. Neutropenia grade 4.*

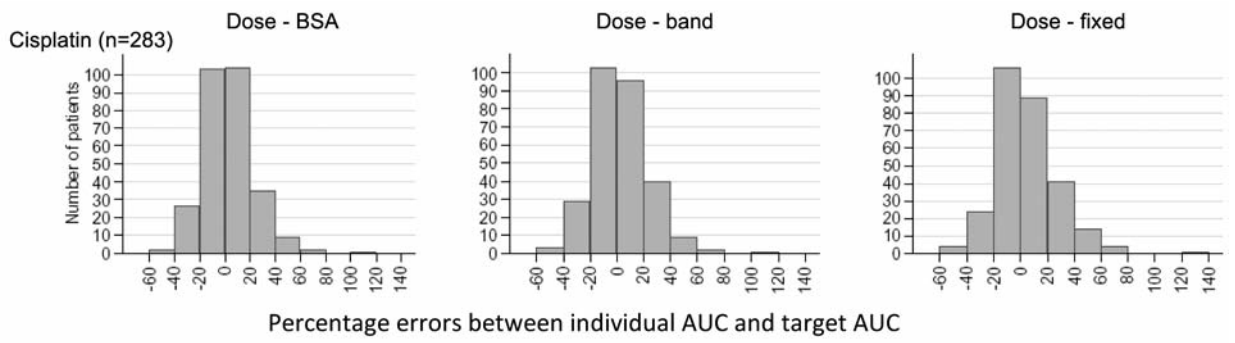

Figure 3. *Frequency of percentage errors between individual AUC and target AUC using BSA dosing, dose banding and fixed dose for cisplatin.*

Considering that BSA-based dosing results in only a small reduction in interpatient variability in drug exposure, the assumption was made that any patient could receive the same fixed dose independently of their morphology. Loos *et al*. compared exposure to unbound cisplatin after a fixed dose and after BSA-adjusted dose in patients with extreme BSA values (26). Fixed doses were determined for a patient with a mean BSA of 1.86 m^2. The AUC of unbound cisplatin was significantly higher after BSA-based dosing compared with fixed dosing (p=0.003) in patients with higher BSA values, and the AUC was significantly lower after BSA-based dosing compared with fixed dosing (p=0.009) in patients with lower BSA values. The authors concluded that a fixed dosing strategy could be associated with a higher risk of toxicity in lean patients and underdosing in obese patients. Hence BSA should be taken into consideration in cisplatin dosing.

Chatelut *et al*. recently proposed an alternative strategy based on clustering patients in three BSA bands (27). By this approach, the dose for a patient is not calculated according to his individual BSA but according to the mid-point of the BSA band. The main advantages of dose banding over current BSA-based dosing would be to allow advanced preparation of chemotherapy, and reduced patient waiting time and improved pharmacy capacity planning. In this retrospective PK study, they simulated doses for 283 patients according to dose-BAND strategy and according to BSA-based dosing (dose-BSA), they then compared individual AUC obtained based on individual CL (AUC=dose/CL) (27). Three BSA bands were determined: BSA <1.7 m^2; 1.7 $m^2 \leq$BSA<1.9 m^2; and BSA≥1.9 m^2. Dose-band corresponded to standard dose (mg/m^2) multiplied by the relevant BSA band value: 1.55 m^2, 1.80 m^2, or 2.05 m^2, respectively. Dose-BSA corresponded to standard dose (mg/m^2) multiplied by individual BSA. Considering that optimal exposure corresponds to the AUC obtained in a patient with a mean observed CL (L/h/m^2) who received a standard dose (mg/m^2), this AUC was designed as target. The efficacy of different dosing strategy was assessed by the absolute relative difference between AUC according to various dosing strategies and target AUC.

For the dose-BSA, the mean absolute relative difference in AUC compared to target AUC was 15.3% [standard deviation (SD)=13.7], whereas it was 15.7% (SD=13.8) for the dose-band (no significantly different). As shown in Figure 3, the repartition of relative difference in AUC across the patients is similar between the two dosing strategies. However, by using a fixed dose, the mean absolute relative difference [*i.e.*, 16.9% (SD=15.8)] would have been significantly higher than that of dose-BSA. Regarding these results it could be concluded that dosing by dose-band is not worse than BSA-based dosing. Even though the dose-band approach does not improve efficacy in comparison with the BSA-based dosing, it offers several substantial advantages in terms of preparation in pharmacy units: chemotherapies can be prepared in advance and pharmacy planning can be improved, reducing the risk of medication error.

Conclusion

For cisplatin, prospective studies are needed to validate the practice of dose banding. For carboplatin, the dose to be given (CL. AUC) may be considered since prediction of carboplatin CL is never perfect.

References

1 Pinkel D: The use of body surface area as a criterion of drug dosage in cancer chemotherapy. Cancer Res *18(7)*: 853-856, 1958.

2 Freireich EJ, Gehan EA, Rall DP, Schmidt LH and Skipper HE: Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep *50(4)*: 219-244, 1966.

3 Yonezawa A, Masuda S, Yokoo S, Katsura T and Inui K: Cisplatin and oxaliplatin, but not carboplatin and nedaplatin, are substrates for human organic cation transporters (SLC22A1-3 and multidrug and toxin extrusion family). J Pharmacol Exp Ther *319(2)*: 879-886, 2006.

4 Elferink F, van der Vijgh WJ, Klein I, Vermorken JB, Gall HE and Pinedo HM: Pharmacokinetics of carboplatin after *i.v.* administration. Cancer Treat Rep *71(12)*: 1231-1237, 1987.

5 van der Vijgh WJ: Clinical pharmacokinetics of carboplatin. Clin Pharmacokinet *21(4)*: 242-261, 1991.
6 Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A and Aisner J: Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum(II) analogue diamminecyclobutanedicarboxylatoplatinum. Cancer Res *45(12 Pt 1)*: 6502-6506, 1985.
7 Lokich J and Anderson N: Carboplatin *versus* cisplatin in solid tumors: an analysis of the literature. Ann Oncol *9(1)*: 13-21, 1998.
8 Benezet S, Guimbaud R, Chatelut E, Chevreau C, Pujol A, Boneu A, Roché H, Houin G and Bugat R: How to predict carboplatin clearance from standard morphological and biological characteristics in obese patients. Ann Oncol *8(6)*: 607-609, 1997.
9 Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roche H, Houin G and Bugat R: Prediction of carboplatin clearance from morphological and biological patient characteristics *87(8)*: 573-580, 1995.
10 Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW and Aisner J: Pharmacokinetics and dosage reduction of cis-diammine(1,1-cyclobutanedicarboxylato) platinum in patients with impaired renal function. Cancer Res *44(11)*: 5432-5438 1984.
11 Schmitt A, Gladieff L, Lansiaux A, Bobin-Dubigeon C, Etienne-Grimaldi MC, Boisdron-Celle M, Serre-Debauvais F, Pinguet F, Floquet A, Billaud E, Le GC, Penel N, Campone M, Largillier R, Capitain O, Fabbro M, Houede N, Medioni J, Bougnoux P, Lochon I and Chatelut E: A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Cancer Res *15(10)*: 3633-3639, 2009.
12 Thomas F, Seronie-Vivien S, Gladieff L, Dalenc F, Durrand V, Malard L, Lafont T, Poublanc M, Bugat R and Chatelut E: Cystatin C as a new covariate to predict renal elimination of drugs: application to carboplatin. Clin Pharmacokinet *44(12)*: 1305-1316, 2005.
13 Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME and Wiltshaw E: Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol *7(11)*: 1748-1756, 1989.
14 Leger F, Seronie-Vivien S, Makdessi J, Lochon I, Delord JP, Sarda C, Canal P and Chatelut E: Impact of the biochemical assay for serum creatinine measurement on the individual carboplatin dosing: a prospective study. Eur J Cancer *38(1)*: 52-56, 2002.
15 Newman DJ: Cystatin C. Ann Clin Biochem *39(Pt 2)*: 89-104, 2002.
16 Belani CP, Kearns CM, Zuhowski EG, Erkmen K, Hiponia D, Zacharski D, Engstrom C, Ramanathan RK, Capozzoli MJ, Aisner J and Egorin MJ: Phase I trial, including pharmacokinetic and pharmacodynamic correlations, of combination paclitaxel and carboplatin in patients with metastatic non-small-cell lung cancer. J Clin Oncol *17(2)*: 676-684, 1999.
17 Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S and Wiltshaw E: Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol *10(4)*: 520-528, 1992.
18 Belani CP, Egorin MJ, Abrams JS, Hiponia D, Eisenberger M, Aisner J and Van Echo DA: A novel pharmacodynamically based approach to dose optimization of carboplatin when used in combination with etoposide. J Clin Oncol *7(12)*: 1896-1902, 1989.
19 Schmitt A, Gladieff L, Laffont CM, Evrard A, Boyer JC, Lansiaux A, Bobin-Dubigeon C, Etienne-Grimaldi MC, Boisdron-Celle M, Mousseau M, Pinguet F, Floquet A, Billaud EM, Durdux C, Le GC, Mazieres J, Lafont T, Ollivier F, Concordet D and Chatelut E: Factors for hematopoietic toxicity of carboplatin: Refining the targeting of carboplatin systemic exposure. J Clin Oncol *20;28(30)*: 4568-74, 2010.
20 Bajorin DF, Bosl GJ, Alcock NW, Niedzwiecki D, Gallina E and Shurgot B: Pharmacokinetics of cis-diamminedichloroplatinum(II) after administration in hypertonic saline. Cancer Res *46(11)*: 5969-5972, 1986.
21 Schellens JH, Ma J, Planting AS, van der Burg ME, van ME, de Boer-Dennert M, Schmitz PI, Stoter G and Verweij J: Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer *73(12)*: 1569-1575, 1996.
22 Urien S and Lokiec F: Population pharmacokinetics of total and unbound plasma cisplatin in adult patients. Br J Clin Pharmacol *57(6)*: 756-763, 2004.
23 de Jongh FE, Verweij J, Loos WJ, de WR, de Jonge MJ, Planting AS, Nooter K, Stoter G and Sparreboom A: Body-surface area-based dosing does not increase accuracy of predicting cisplatin exposure. J Clin Oncol *19(17)*: 3733-9, 2001.
24 de Jongh FE, Gallo JM, Shen M, Verweij J and Sparreboom A: Population pharmacokinetics of cisplatin in adult cancer patients. Cancer Chemother Pharmacol *54(2)*: 105-112, 2004.
25 Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J and Baker SD: Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol *20;25(30)*: 4707-4713, 2007.
26 Loos WJ, de Jongh FE, Sparreboom A, de WR, van Boven-van Zomeren DM, Stoter G, Nooter K and Verweij J: Evaluation of an alternate dosing strategy for cisplatin in patients with extreme body surface area values. J Clin Oncol *24(10)*: 1499-1506, 2006.
27 Chatelut E, White-Koning ML, Mathijssen RH, Puisset F, Baker SD and Sparreboom A: Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents. Br J Cancer *107(7)*: 1100-1106, 2012.

Received August 20, 2013
Revised November 25, 2013
Accepted November 27, 2013