Abstract

Purpose: It has recently been shown that it is possible to improve the prediction of carboplatin clearance by adding plasma cystatin C level (cysC), an endogenous marker of glomerular filtration rate, to the other patient characteristics routinely used for carboplatin individual dosing, namely serum creatinine (Scr), actual body weight (ABW), age, and sex. This multicenter pharmacokinetic study was done to evaluate prospectively the benefit of using cysC for carboplatin individual dosing.

Experimental Design: The 357 patients included in the study were receiving carboplatin as part of established protocols. A population pharmacokinetic analysis was done using NONMEM program. Seven covariates studied were as follows: Scr, cysC, age, sex, ABW, ideal body weight, and lean body mass.

Results: The best covariate equation was as follows: carboplatin clearance (mL/min) = 117.8. (Scr/75)^−0.450. (cysC/1,00)−0.385. (ABW/65)+0.504. (age/56)−0.366. (age/56)−0.366. (age/56)−0.366. (age/56), with Scr in μmol/L, cysC in mg/L, ABW in kilograms, age in years, and sex = 0 for male. Using an alternative weight descriptor (ideal body weight or lean body mass) did not improve the prediction. This final covariate model was validated by bootstrap analysis. The bias (mean percentage error) and imprecision (mean absolute percentage error) were +1% and 15%, respectively, on the total population, and were of a similar magnitude in each of the three subgroups of patients defined according to their body mass index.

Conclusion: For the first time, a unique formula is proposed for carboplatin individual dosing to patients, which is shown to be equally valid for underweight, normal weight, and obese patients.

Carboplatin elimination is very dependent on glomerular filtration rate (GFR; ref. 1). Several formulae are used for individual carboplatin dosing. The first was developed by Egorin et al. (2) using the measured creatinine clearance (CrCl; requiring 24-hour urine collection). Some years later, Calvert et al. (3) proposed to use the GFR measured by the clearance (CL) of \([\text{Cr}^{51}]\)EDTA. Since then, substituting the CrCl calculated with the Cockcroft-Gault equation (4) into the Calvert formula (i.e., carboplatin CL = CrCl + 25) is the most widely used method to calculate the individual dose of carboplatin. Over the past 15 years, there has been an endless debate concerning the best equation to predict carboplatin CL. No single equation has been found to be applicable to all patients without bias except for the original method based on \([\text{Cr}^{51}]\)EDTA CL determination (5). The main limitation of the existing equations is that they are all based on serum creatinine level (Scr) as the unique biological covariate (together with demographical and morphologic covariates). Scr is dependent on GFR, but its rate of production depends on muscle mass. Because of this, it has been shown that several of the existing formulae overestimate carboplatin CL in both obese patients and patients with cachexia (6). Recently, Thomas et al. (7) showed by analyzing the pharmacokinetic data of 45 patients from one center that cystatin C plasma level (cysC) was a marker of carboplatin elimination that is at least
Translational Relevance

Individual dosing of carboplatin is a current practice to control plasma drug exposure of this drug. The main limitation of the existing equations is that they are all based on serum creatinine level as the unique biological covariate; it has been shown that these formulae overestimate carboplatin clearance in both obese patients and patients with cachexia. Cystatin C plasma level has been suggested as an endogenous marker of glomerular filtration rate. The results of this prospective multicentric pharmacokinetic clinical study validate an equation based on five parameters (Scr, cystatin C, actual body weight, age, and sex), which is shown to be equally valid for underweight, normal weight, and obese patients.

Patients and Methods

Patients. The 357 patients with various cancers who were included in this study came from 10 different centers and were receiving carboplatin as part of established protocols either as a single agent (70 patients) or in combination with paclitaxel (194 patients), etoposide (31 patients), gemcitabine (17 patients), vinorelbine (10 patients), doxorubicin (9 patients), docetaxel (6 patients), fluorouracil (7 patients), or other drugs (11 patients). The primary tumor sites were ovary (156 patients), uterus (44 patients), lung (36 patients), head and neck (11 patients). The primary tumor sites were ovary (156 patients), uterus (44 patients), lung (36 patients), head and neck (15 patients), and other (106 patients). The main patient characteristics are shown in Table 1. The pharmacokinetic protocol was approved by the ethical committee of Toulouse I, and informed written consent was obtained from each patient.

Carboplatin administration, blood sampling, and platinum analysis. Carboplatin was administered as a daily 30- or 60-min infusion in 5% dextrose at doses ranging from 170 to 1,600 mg (mean, 557 mg). Either Calvert formula with Cockcroft-Gault equation, Chatelut formula (8), or body surface area was used for carboplatin dose individualization depending on the Centers and the regimen. Four blood samples were taken at the first treatment cycle: at time 0 (before administration), 5 min before the end of the infusion, and at 1 and 4 h after the end of the infusion. The latter three samples were selected according to a limited sampling strategy developed previously (9). After immediate centrifugation at 1,500 g for 10 min at 4°C, the plasma was separated and ultrafiltered using the Amicon MPS1 micropartition system with YMT membranes at 4°C for 20 min at 2,000 g. Carboplatin levels in the plasma ultrafilterate were measured by means of flameless atomic absorption spectrophotometric analysis according to a previously described method (10) in six laboratories. A cross-validation procedure was done previously. The coefficients of variation for precision using spiked plasma ultrafiltrate control samples with nominal values of 100, 3,000, and 90,000 ng/mL were 4.30%, 2.26%, and 7.18%, respectively. Each laboratory obtained a value within the interval ±20%, ±10%, and ±10%, for the low, medium, and high control sample, respectively. These intervals were those used for validation of each run in each laboratory.

Biochemical analyses. Scr was measured in each center by several methods (i.e., Jaffé, Jaffé modified, spectoreflectometric, and enzymatic method). CysC plasma level was measured from a frozen serum sample by an automated particle-enhanced nephelometric immunoassay at the Institut Claudius-Renard. The analyzer (BN-ProSpec), as well as the controls, standards and kits (N Latex cysC) were provided by Dade-Behring.

Pharmacokinetic analysis. Data were analyzed using the NONMEM program (version VI, level 1.0, Icon Development Solutions, running on Intel Xeon) according to a two-compartment pharmacokinetic model and first-order conditional estimation with interaction method. A proportional error model was used for both residual and interpatient variability.

Determination of the individual pharmacokinetic parameters. Because the limited sampling strategy used for the present study did not enable us to estimate accurately the distribution parameters (Vc, Vp, and Q for central and peripheral volumes, and intercompartment CL, respectively), the carboplatin concentrations versus time data were combined with a database composed of those values from 143 patients with rich sampling (9, 11): 7 samples (on average) per patient (their detailed characteristics are given in Table 1). Typical values of Vc and Vp were both proportional to body surface area. No covariate was considered for the typical value of both CL and Q. Individual pharmacokinetic parameters were obtained by Empirical Bayes estimation using the POSTHOC option. A component for each center was included in the residual error model. Individual values of Vc, Vp, and Q for the 357 patients in the present study were assigned to each patient for the covariate analyses on CL (i.e., Vc, Vp, and Q were not estimated during the covariate testing). Individual CLs were considered as the observed values to be compared with the values predicted from the covariate model.

Covariate analyses. The coefficients and exponents corresponding to the Thomae formula (ref. 7; i.e., CL = β1 * (Scr/75)β2 * (cysC/1.0)β3 * (actual body weight (ABW)/65)β4 * (age/56)β5 * (sex, with Scr in μmol/L, cysC in mg/L, ABW in kilograms, age in years, and sex = 0 for male)) were determined by analyzing only the plasma carboplatin concentrations versus time from the 357 patients in the present study (first-order conditional estimation with interaction method). The significance of the contribution of each of the five covariates in the Thomas formula was assessed by backward elimination of each covariate from the full model. Full and reduced models (one parameter less) were compared using a χ² test of difference between their respective objective function values (OBJ). Objective function value is equal to minus twice the log likelihood of the data. This value is an indicator of the goodness of fit of the model. A change of at least 10.8 (P < 0.001, 1 degree of freedom) was required to consider the covariate as significant. Ideal body weight (49.9 + 0.89 *[height (cm) – 152.4]) for male, 45.4 + 0.89 *[height (cm) – 152.4] for female), and lean body mass (1.1 * ABW – 0.0128 * BMI * ABW for male, 1.07 * ABW –
evaluated by computing the mean percentage error \( mpe = \frac{\sum_{j=1}^{n} \left| \frac{Cl_{\text{observed}} - Cl_{\text{predicted}}}{Cl_{\text{predicted}}} \right| \times 100}{n} \) as a measure of bias and the mean absolute percentage error \( mape = \sum_{j=1}^{n} \left| \frac{Cl_{\text{observed}} - Cl_{\text{predicted}}}{Cl_{\text{predicted}}} \right| \times 100 \) as an assessment of imprecision.

### Results

#### Determination of the individual pharmacokinetic parameters.

The 1,057 carboplatin-ultrafiltrable plasma concentrations from the 357 patients in the present study ranged between 0.44 and 69.16 mg/L (median, 13.34 mg/L). A bicomartmental structural model was used to describe the pharmacokinetic of carboplatin. It was found to describe data very accurately on June 29, 2017. © 2009 American Association for Cancer Research.

Universal Formula for Individual Dosing of Carboplatin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study population mean (range)</th>
<th>Database mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 (21-87)</td>
<td>60 (23-84)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65 (40-137)</td>
<td>68 (40-112)</td>
</tr>
<tr>
<td>Body surface area (m²)*</td>
<td>1.70 (1.30-2.37)</td>
<td>1.75 (1.28-2.24)</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>77 (25-433)</td>
<td>108 (55-353)</td>
</tr>
<tr>
<td>Serum cysC (mg/L)</td>
<td>0.90 (0.44-3.49)</td>
<td>NA</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>80 (10-216)</td>
<td>67 (14-168)</td>
</tr>
</tbody>
</table>

Note: Patients, \( n = 357 \) (female/male, 264/93); 143 patients corresponding to the database with rich sampling (female/male, 88/55).

Abbreviation: NA, not available.

*Calculated according to the Dubois equation.

*Calculated according to the Cockcroft-Gault equation.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study population mean (range)</th>
<th>Database mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 (21-87)</td>
<td>60 (23-84)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65 (40-137)</td>
<td>68 (40-112)</td>
</tr>
<tr>
<td>Body surface area (m²)*</td>
<td>1.70 (1.30-2.37)</td>
<td>1.75 (1.28-2.24)</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>77 (25-433)</td>
<td>108 (55-353)</td>
</tr>
<tr>
<td>Serum cysC (mg/L)</td>
<td>0.90 (0.44-3.49)</td>
<td>NA</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>80 (10-216)</td>
<td>67 (14-168)</td>
</tr>
</tbody>
</table>

Note: Patients, \( n = 357 \) (female/male, 264/93); 143 patients corresponding to the database with rich sampling (female/male, 88/55).

Abbreviation: NA, not available.

*Calculated according to the Dubois equation.

*Calculated according to the Cockcroft-Gault equation.

0.0148*BMI*ABW for female) were tested as an alternative weight descriptor. As for the determination of the individual pharmacokinetic parameters, a component for each center was included in the residual error model.

**Bootstrap evaluation of the population pharmacokinetic model.**

A nonparametric bootstrap analysis was done as an internal model evaluation technique, using the package Wings for NONMEM (version 614). A new replication of the original data set (a bootstrap sample) was obtained by \( n \) random draws of individual data (with replacement) from the original data set (\( n = 357 \)). The final population pharmacokinetic model was refit to each new data set, and this process was repeated 1,000 times with different random draws. To validate the model, the parameters estimated from the bootstrap had to be close to the estimates obtained from the original population set.

**Performance of the final pharmacokinetic model.**

The carboplatin CL values obtained with the final covariate model were compared with the values of the 4 covariates changed by -12% (for Scr), +18% (for cysC), +6% (for ABW), and -5% (for age); the sex factor (i.e., 0.85) was identical. Deletion of each of the 5 covariates from this covariate model was associated with a significant (\( P < 0.001 \)) increase of the objective function value (+34, +54, +62, +75, and +79 for sex, age, cysC, Scr, and ABW deletion, respectively) showing that this equation (the modified Thomas formula) should be considered as the final covariate model. A worst adjustment of the plasma carboplatin concentrations (i.e., increase of the objective function value) was observed when ideal body weight or lean body mass was used as weight descriptor within the equation. Figure 2 shows the correlation between observed carboplatin CL of the 357 patients and CL as calculated by the modified Thomas formula.

**Bootstrap evaluation of the modified Thomas formula.**

The final model [i.e., \( Cl = 0.1(\text{Scr}/75)^{0.2}(\text{cysC}/1.0)^{0.3}(\text{ABW}/65)^{0.4}(\text{age}/56)^{0.6}\)] was subjected to a bootstrap analysis. Bootstrap runs with unsuccessful minimization were excluded (2 of 1,000). The mean parameter estimates obtained from the 998 bootstrap runs with unsuccessful minimization were almost identical to the estimates previously obtained with the original data set (Table 2).

**Performance of the final pharmacokinetic model.**

Table 3 gives the bias (mpe) and imprecision (mape) corresponding to the modified Thomas formula together with those of the Calvert formula using CrCl estimated from Cockcroft-Gault equation. Fifth 95th percentiles of the percentage errors are also given. As
a further indication of performance, the percentage of patients poorly estimated (i.e., with absolute percentage error larger than 20%) is presented for all patients and for each of the subgroups of patients defined according to their BMI. Detailed distributions of the percentage errors of carboplatin CL prediction are shown in Fig. 3. To reveal any possible bias of the modified Thomas formula, mpe values were determined for several subgroups of patients defined according to other characteristics. No significant difference was observed between untreated (n = 221) versus pretreated patients (n = 136; mpe of −1.4% versus +3.8%, respectively), 0 performance status (n = 169) versus 1-2-3 performance status (n = 188; mpe of +1.7% versus −0.4%), CrCl of <50 mL/min (n = 43) versus CrCl of ≥50 mL/min (n = 314; mpe of −4.0% versus +1.2%), and between the 10 centers (the 10 mpe values ranged from −10.1% to +12.6%). We found no significant relationship between the creatinine assay used in each center and the distribution of mpe values (the previous two extreme values were from the same assay).

Discussion

Because carboplatin is poorly correlated with body surface area, but linearly related to GFR, the principle of individual dosing based on renal function is largely accepted for this drug. Substitution of GFR by the estimated CrCl as calculated by the Cockcroft-Gault equation is the most widely used method. The pharmacokinetic studies comparing other formulae used to predict individual carboplatin CL have shown conflicting results, despite all being based on the same patient characteristics (i.e., Scr, ABW, age, and sex; refs. 13–17). It seems that none of these equations gives good predictions in all patients. Ekhart et al. (5) went as far as recommending the administration of a flat dose of carboplatin rather than using any of these formulae in patients with normal function or mild renal impairment (defined as those with CrCl of >50 mL/min) because they observed no significant correlation between observed and predicted carboplatin CLs regardless of the formula used [i.e.,

![Figure 1](image-url)
Cockcroft-Gault (4), Jelliffe (18), or Wright (19) equation to estimate CrCl, or Chatelut equation (8) to predict directly carboplatin CL. As pointed out by these authors, the main limitation of all these formulae is that they are based on Scr. First, the intermethod imprecision of Scr assays is relatively important. In a report comparing 17 methods of measuring Scr, the intermethod coefficient of variation was as high as 25% (20). Moreover, Scr is also dependent on nonrenal factors, especially creatinine production, which itself depends on muscle mass. As shown by Herrington et al. (6), formulae based on Scr to predict carboplatin CL are biased in both obese patients and cachectic patients. In obese patients, the high ABW/Scr ratio is associated with a larger predicted carboplatin CL, whereas their carboplatin CL are biased in both obese patients and cachectic patients. In cachectic patients, the low Scr and therefore their carboplatin CL is no larger than that of a normal patient. Cachectic patients have a low Scr and therefore their carboplatin CL prediction in comparison with ABW.

Table 2. Typical estimates (and 95% confidence interval) obtained by NONMEM analysis and the 1,000 bootstrap replicates for the modified Thomas formula

<table>
<thead>
<tr>
<th>CL (mL/min) = 81.(Scr/75)(^{0.2}). (cysC/1.0)(^{0.38}). (ABW/65)(^{0.50}). (age/56)(^{-0.36}). 0.84(^\text{SEX} )</th>
<th>NONMEM analysis</th>
<th>Bootstrap analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 117.8 (112.1-123.5)</td>
<td>117.8 (112.4-123.2)</td>
<td></td>
</tr>
<tr>
<td>82 -0.450 (-0.551 to -0.349)</td>
<td>-0.452 (-0.555 to -0.349)</td>
<td></td>
</tr>
<tr>
<td>83 -0.368 (-0.505 to -0.265)</td>
<td>-0.365 (-0.508 to -0.263)</td>
<td></td>
</tr>
<tr>
<td>84 +0.504 (+0.396 to +0.612)</td>
<td>+0.505 (+0.398 to +0.612)</td>
<td></td>
</tr>
<tr>
<td>85 -0.368 (-0.449 to -0.283)</td>
<td>-0.368 (-0.450 to -0.286)</td>
<td></td>
</tr>
<tr>
<td>86 0.847 (0.802-0.892)</td>
<td>0.848 (0.805-0.891)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Scr, μmol/L; cysC, plasma cysC (mg/L); ABW, kilograms; age, y; sex = 0 for male, 1 for female.
found for the whole data set (mpe, +1%; mape, 14%), with only 21% of the patients with an absolute percentage error of >20% (corresponding values for Calvert formula based on Cockcroft-Gault equation were as follows: mpe, −6%; mape, 17%; and 30% of patients poorly predicted). Again, the use of cysC reduces the bias due to low values of Scr.

Moreover, we did not observe any significant bias between patients defined by other characteristics (pretreatment, performance status, and renal function). All these results indicate that cysC compensates the limitations of Scr and gives a more universal formula to predict carboplatin CL. Therefore, we think cysC deserves to be determined for individual dosing of carboplatin. Unfortunately, this assay is currently available in a limited number of biochemistry laboratories. However, there is extensive scientific literature concerning cysC with 288 references during the past year, most of them dealing with cysC as a marker of renal function. There are currently three methods used to measure cysC: particle-enhanced nephelometric immunoassay (method used in our study), particle-enhanced turbidimetric immunoassay, and ELISA. Particle-enhanced turbidimetric immunoassay and particle-enhanced nephelometric immunoassay give very similar results, but ELISA values require a normalization by a factor 0.66 to be consistent with the other 2 methods (22).

![Figure 3. Number of patients versus percentage errors between predicted and observed carboplatin CL using either the modified Thomas formula or Calvert formula based on Cockcroft-Gault equation in subgroups defined according to BMI (hatched bars, patients with absolute percentage error larger than 20%).](image-url)

### Table 3. Comparison between the modified Thomas formula and the Calvert formula based on Cockcroft-Gault equation for all, obese, normal weight, and underweight patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>mape (%)*</th>
<th>mpe (%)†</th>
<th>5th percentile (%)</th>
<th>95th percentile (%)</th>
<th>% of patients with absolute percentage error &gt; 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thomas</td>
<td>Calvert</td>
<td>Thomas</td>
<td>Calvert</td>
<td>Thomas</td>
</tr>
<tr>
<td>All (n = 357)</td>
<td>15</td>
<td>17</td>
<td>+1</td>
<td>−6</td>
<td>25</td>
</tr>
<tr>
<td>Obese (n = 43)</td>
<td>12</td>
<td>14</td>
<td>−3</td>
<td>+1</td>
<td>−28</td>
</tr>
<tr>
<td>Normal weight (n = 285)</td>
<td>15</td>
<td>18</td>
<td>+1</td>
<td>−7</td>
<td>−24</td>
</tr>
<tr>
<td>Underweight (n = 29)</td>
<td>15</td>
<td>21</td>
<td>−2</td>
<td>−11</td>
<td>−33</td>
</tr>
</tbody>
</table>

*Mean absolute percentage error as a measure of precision.
†Mean percentage error as a measure of bias.
In conclusion, the modified Thomas formula is the first equation enabling individual area under the curve dosing of carboplatin in obese and underweight patients with a minimal bias. However, it should be emphasized that the proposed formula may only be applied to patients having characteristics within the range of the present population (e.g., age, 21–87 years; ABW, 40-137 kg; Scr, 25-433 μmol/L). We recommend the use of the particle-enhanced nephelometric immunoassay or particle-enhanced turbidimetric immunoassay method to determine cysC for individual carboplatin dosing. Lastly, because carboplatin elimination is highly dependent on renal function, the benefit of considering cysC for individual dosing should also exist for other renally cleared drugs such as topotecan in Oncology (23), and aminoglycosides in Infectious Diseases (24).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Emmanuelle Bourbouloux, Patrick Soulé, and Erick Gamelin as clinical investigators; Thierry Lafont, Stéphanie Clisant, and Christine Bal-Mahieu for technical assistance; Florent Ollivier for monitoring of the study; and Mélanie White-Koning for editorial assistance with the English.

References


www.aacrjournals.org


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Emmanuelle Bourbouloux, Patrick Soulé, and Erick Gamelin as clinical investigators; Thierry Lafont, Stéphanie Clisant, and Christine Bal-Mahieu for technical assistance; Florent Ollivier for monitoring of the study; and Mélanie White-Koning for editorial assistance with the English.
A Universal Formula Based on Cystatin C to Perform Individual Dosing of Carboplatin in Normal Weight, Underweight, and Obese Patients
