Pharmacokinetics of low-dose carboplatin and applicability of a method of calculation for estimating individual drug clearance

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Background: Carboplatin is the only cancer drug for which conventional doses are individually adjusted according to estimated clearance and target area under the curve (AUC). The aim of this prospective study was (i) to evaluate intra- and interpatient variability of ultrafilterable (UF) carboplatin AUC₀–∞ and (ii) to test whether the prediction of carboplatin clearance according to the Chatelut formula established for conventional carboplatin doses was accurate for low carboplatin doses.

Materials and methods: Thirty-one head and neck cancer patients (29 men, two women, mean age 55.9 years) received concomitant radiotherapy (Rγ 2 Gy/day) and chemotherapy (carboplatin 50 mg/m²/day i.v.) for 7 weeks: Rγ was administered 5 days/week (days 1–5) and carboplatin 2 days/week (days 1 and 4). Pharmacokinetics was performed once per week. A limited sample strategy based on Bayesian analysis was first validated and blood was subsequently taken 1 and 4 h after the end of carboplatin administration.

Results: A total of 143 cycles was analyzed. Ultrafilterable carboplatin AUC₀–∞ ranged from 0.360 to 4.200 mg·min/ml (mean 0.830, median 0.670). As a corollary, UF carboplatin clearance ranged from 19.1 to 244.7 ml/min. Ultrafilterable carboplatin concentrations were very stable over time: AUC₀–∞ variability due to treatment duration contributed to <1% of the total variance, while interpatient variability contributed to 68.6%. Accordingly, intrasubject effect was not significant (P = 0.38) whereas intersubject effect was highly significant (P <0.001). These results suggest that optimal dosage for targeting a given AUC may vary within a 13-fold range between patients. The Chatelut formula, based on creatininemia, body weight, age and sex, overestimates carboplatin clearance by 40% on average (bias 95% CI 29.6% to 51.1%). No significant relationship was observed between either bone marrow toxicity or creatinine clearance decrease and carboplatin pharmacokinetics.

Conclusions: The Chatelut carboplatin clearance model established for conventional carboplatin dosages (>100 mg/m²) is not applicable for targeting low AUC (<1 mg·min/ml).

Key words: carboplatin disposition, Chatelut formula, head and neck cancer, low-dose carboplatin, pharmacokinetic, radiotherapy

Introduction

The area under the curve (AUC)-based dosing strategy for carboplatin is well supported by several published studies, having shown correlations between exposure to carboplatin and toxicity or tumor response [1–3]. Of particular interest was the fact that carboplatin clearance could be individually predicted on the basis of individual variables, thus making it possible to administer the appropriate dose to a given subject to obtain a fixed AUC [3]. This strategy was made feasible by applying formulae that permit estimation of carboplatin clearance and to individually calculate carboplatin dose. Calvert et al. [4] and Chatelut et al. [5] illustrate this point. The clinical validation of this approach has been recently established [6]. The authors of this latter study conducted a randomized cross-over trial in children with cancer and demonstrated that renal function based carboplatin dosing is more precise than surface area based drug administration.

Other studies indicate that these methods of calculation for estimating carboplatin AUC are also applicable to high carboplatin exposures [7], although this view is not unanimously shared [8]. In head and neck cancer, given the limited results of radiotherapy alone, the association of conventional once-a-day radiotherapy with platinum analogs, including carboplatin, has been extensively explored [9–13], as well as combinations with other cytotoxic drugs. Our institute is strongly involved in this multidisciplinary therapeutic strategy [14]. A meta-analysis published in 1996 [15] clearly showed a benefit, in terms of loco-regional control in head and neck cancer, for combined treatment as compared with radiotherapy alone. Another more recent meta-analysis [16] has confirmed these conclusions with an absolute
benefit of 4% in 5-year survival for patients receiving chemoradiotherapy, this benefit being 2-fold higher (8%) when concomitant chemoradiotherapy was administered. Thus, chemoradiotherapy is currently becoming a standard in induction therapy for advanced head and neck cancer patients. This treatment approach is also promising for the management of advanced cervical cancer [17]. One means of limiting the unavoidable side-effects linked to this treatment is to reduce the interpatient variability in drug exposure. A valuable approach to reach this objective would be to apply an AUC-targeted strategy when carboplatin is the platinum analog associated with radiotherapy. The purpose of this prospective study was thus to examine the distribution of carboplatin AUC values in a group of 31 head and neck cancer patients treated by low-dose carboplatin (143 cycles analyzed) in concomitant association with radiotherapy, and to evaluate whether the Chatelut’s formula is applicable to this specific situation of low-dose carboplatin combined with radiotherapy.

**Materials and methods**

**Patients**

This prospective pharmacokinetic and pharmacological study was conducted at the Centre Antoine Lacassagne on a homogeneous group of patients receiving adjuvant postoperative concomitant radio- and chemotherapy in histologically proven epidermoid head and neck carcinoma with node involvement. A total of 31 patients was analyzed (29 men, two women; mean age 55.9 years, range 48–78 years; mean body weight 65 kg, range 48–90 kg). Tumor sites were oropharynx, hypopharynx and larynx for 19, four and eight patients, respectively. All patients had a World Health Organization performance status of 2. Treatment started 4–9 weeks after surgical resection and consisted of concomitant radio- and chemotherapy for 6–7 weeks (1 cycle each week): radiotherapy (Ry 2 Gy/day) was applied 5 days/week (days 1–5) and carboplatin was applied 2 days/week (50 mg/m²/day, 20 min i.v., on days 1 and 4, 2 h before radiotherapy). Carboplatin administration was suspended in cases of neutropenia (leukocytes <1000/mm³), thrombocytopenia (platelets <90000/mm³), hemorrhage, grade 4 infection, or any other severe side-effect. Creatinemia, ionogram, blood count, body weight and clinical tolerance were checked every week. Carboplatin pharmacokinetics was performed once per week on day 1.

Radio- and chemotherapy-related toxicities were recorded at each cycle, according to the International Union Against Cancer (UICC) criteria. Renal function was evaluated before each cycle, by estimating creatinine clearance (CC) according to the Cockcroft formula [18]: CC (ml/min) = (140 – age) × body weight (kg)/[0.8 × serum creatinine (µM)]. For women, a factor of 0.85 was applied. The relative decrease of CC at cycle i as compared with CC measured before starting carboplatin was then defined as 100 × (CC cycle 1 – CC cycle i)/CC cycle 1.

**Sampling strategy and pharmacokinetics analyses**

A limited sampling strategy based on Bayesian analysis using the NONMEM program (previously developed with data obtained after carboplatin administration at conventional doses [19]) was first validated on the first six patients (20 cycles) treated at low doses. For that purpose, extended blood sampling was performed on completion of the carboplatin 15-min infusion, and 1, 4, 6 and 8 h after the end of carboplatin administration. Ultrafilterable (UF) carboplatin plasma concentrations from these six patients (20 cycles) were combined with a database composed from 103 patients; no covariate was taken into account in order to obtain individual carboplatin AUC (by first-order conditional estimation). This validated limited sampling strategy led to the adoption, for subsequent patients, of a limited blood sampling 1 and 4 h following carboplatin administration.

Ultrafilterable carboplatin systemic clearance (CL) was defined as carboplatin total dose divided by UF carboplatin AUC₀–∞.

**Carboplatin analysis**

Blood samples (5 ml in EDTA tubes) were immediately placed in a water bath containing ice for transportation (within 15 min) to the laboratory and centrifuged for 10 min at 4°C. 500 µl of the resulting plasma was then centrifuged for 30 min (2000 g at 4°C) in a Centrifuge microvaporization unit (Amicon, Denver, MA, USA) in order to obtain UF carboplatin. Ultrafiltrate samples were stored at -20°C until analysis.

UF carboplatin was measured by means of atomic absorption spectroscopy using a Perkin–Elmer 3030 with background correction by the Zeeman effect. UF samples taken at 1 and 4 h were diluted 1:10 and 1:2, respectively, in 0.9% NaCl. The injected volume was 20 µl. Measured platinum concentrations were recalculated as carboplatin levels. Concentrations and AUC were thus expressed as the carboplatin levels. The standard curve was automatically performed (0, 308, 618 and 1236 ng/ml). The limit of sensitivity was 20 ng/ml. Interassay variability was evaluated by analysis of spiked samples containing 100 and 400 ng/ml carboplatin, respectively; coefficients of variation were 9.8% and 6.9%, respectively, from 11 consecutive analyses.

**Statistics**

Statistics were performed on SPSS software (Chicago, IL, USA). AUC₀–∞ did not fit the normal distribution and was thus analyzed as logarithm 10, which fitted the Gaussian law. Two types of analyses of variance were performed for AUC₀–∞ on the group of 23 patients with pharmacokinetics available from cycle 1 to cycle 5: (i) a component variance analysis to assess respective variance contributions; and (ii) a repeated measures analysis to test intra- and intersubjects effects.

An analysis of variance of the relative decrease of CC was performed with log AUC₀–∞ as covariate, subject as random effect and cycle number as fixed factor, in order to analyze the possible influence of carboplatin cycle and pharmacokinetics on the renal function.

The applicability of the Chatelut formula [5] for predicting CL was assessed by computing the bias defined as 100 × (predicted CL – observed CL)/observed CL. The link between the above-defined bias and the observed CL was subsequently analyzed by means of Spearman rank correlation.

**Results**

**Validation of the limited sample strategy**

AUC values obtained by limited sampling (1 and 4 h following completion of carboplatin administration) were compared with those resulting from extensive sampling (i.e. five samples per patient and per cycle). Absolute percentage error between the AUC from two samples on one hand, and from all samples on the other, was <20% for 18 of 20 cycles, including extended sampling. The root mean squared relative prediction error (as assessment of precision) corresponding to these 18 cycles was 10%.

**Analysis of carboplatin AUC during the treatment course**

A total of 143 cycles was analyzed (Table 1). Carboplatin doses actually administered closely fitted those initially planned (mean 49.5 mg/m², range 43–53). UF carboplatin AUC₀–∞ exhibited
wide variability, with values ranging from 0.360 to 4.200 mg·min/ml (mean 0.830, median 0.670, first–third quartile 0.535–0.890). As a corollary, CL ranged from 19.1 to 244.7 ml/min (mean 130, median 132, first–third quartile 97.5–164.3). Figure 1 illustrates the marked interpatient variability in AUC\(_0^\infty\) values.

Component variance analysis of AUC\(_0^\infty\) showed that variability due to treatment duration contributed to <1% of the total variance while that due to interpatient variability contributed to 68.6% (residual variance represented 31.3%). Accordingly, repeated measures analysis of AUC\(_0^\infty\) demonstrated that treatment duration (intrasubjects effect) was not significant (P = 0.38), whereas intersubjects effect was highly significant (P <0.001).

### Table 1. Description of ultrafilterable carboplatin AUC\(_0^\infty\) according to the chemotherapy cycle

<table>
<thead>
<tr>
<th>Cycle</th>
<th>n</th>
<th>AUC(_0^\infty) (mg·min/ml)</th>
<th>Mean(^a)</th>
<th>Median(^a)</th>
<th>95% CI</th>
<th>SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>0.715</td>
<td>0.596</td>
<td>0.591–0.865</td>
<td>0.622 (0.379–3.325)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>0.790</td>
<td>0.771</td>
<td>0.658–0.949</td>
<td>0.715 (0.359–4.196)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>0.748</td>
<td>0.646</td>
<td>0.629–0.890</td>
<td>0.404 (0.423–1.926)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>0.744</td>
<td>0.675</td>
<td>0.607–0.913</td>
<td>0.689 (0.393–3.207)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>0.674</td>
<td>0.656</td>
<td>0.585–0.776</td>
<td>0.247 (0.388–1.315)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>0.693</td>
<td>0.701</td>
<td>-(^b)</td>
<td>0.156 (0.552–0.879)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0.820</td>
<td>-(^b)</td>
<td>-(^b)</td>
<td>-(^b) (0.648–1.036)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Means, medians and 95% confidence intervals were computed from log 10-transformed data (i.e. correspond to arithmetical descriptors).

\(^b\)Indicates not assessable due to the small number of cases.

CI, confidence interval; SD, standard deviation.

### Application of the Chatelut formula

For each cycle, we estimated the CL using the Chatelut model established for conventional carboplatin dosages. The mean predicted CL arising from this model was 160.7 ml/min (median 163, range 44.6–279.2, 143 cycles analyzed). Intra-individual analysis of the bias showed that the Chatelut formula overestimates CL by 40% on average (n = 143, mean bias 40.4%, median 24%, 95% CI 30% to 51%, extremes –43% to 336%). Similar bias was observed when considering only the first chemotherapy cycle (n = 31, mean bias 44.3%). The poor applicability of the Chatelut formula in the present situation of low-dose administration is illustrated in Figure 2. Of note, a strong correlation was demon-

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**Figure 1.** Individual plots of the evolution of ultrafilterable carboplatin AUC\(_0^\infty\) according to the carboplatin cycle (31 patients analyzed). Pharmacokinetics was evaluated once a week (1 cycle was equivalent to 1 week). *Patient 18.

**Figure 2.** Plot of the predicted carboplatin clearance (CL) (estimated from the Chatelut model) versus the observed carboplatin CL, for the 143 cycles analyzed (Pearson correlation \(r^2 = 0.35\), P <0.001).
AUC0 mg pharmacokinetics. 10 grade 3); none of these toxicities was related to carboplatin and mucositis in 54.5% of cycles (38 grade 1, 30 grade 2, observed in 57.3% of cycles (55 grade 1, 22 grade 2, five grade 3) were not related to carboplatin pharmacokinetics. However, intra-individual analysis of the bias showed that the Chatelut formula overestimated CL by 40% on average. A strong correlation was demonstrated between bias and observed CL: the lower the observed CL the greater the bias (Spearman rank correlation, \( r^2 = 0.47, P < 0.001 \); Figure 3).

**Pharmacokinetic–pharmacodynamic relationships**

Side-effects were recorded for the 143 cycles. This radio-chemotherapy regimen was well tolerated at the hematological level; no severe thrombocytopenia or neutropenia was observed. Anemia was observed in 9.1% of cycles with a majority of grade 1 (10 grade 1, three grade 3). Grade 3 anemia was observed at cycle 2 for patient 18, who exhibited the highest AUC∞ (4.200 mg·min·ml, and at cycles 4 and 5 for a patient with moderate AUC∞ (0.393 and 0.482 mg·min·ml, respectively). Nausea (10 grade 1, three grade 2, one grade 3) and vomiting (one grade 1, two grade 2, one grade 3) were not related to carboplatin pharmacokinetics.

No clinical nephrotoxicity was observed. Renal function was evaluated before each cycle, by estimating CC according to the Cockcroft formula [18]. The relative decrease of CC was quite stable during the treatment course (mean –0.2%, median 0%, range –80% to 62%). Analysis of variance demonstrated that the relative decrease of CC during treatment was not related to carboplatin cycle \( P = 0.69 \), nor to carboplatin AUC∞ \( P = 0.97 \). However, it is interesting to note that for patient 18, with the highest AUC∞, CC was 62.1 and 23.8 ml/min at cycles 1 and 2, respectively.

Limiting toxicity was related to radiotherapy, with dermatitis observed in 57.3% of cycles (55 grade 1, 22 grade 2, five grade 3) and mucositis in 54.5% of cycles (38 grade 1, 30 grade 2, 10 grade 3); none of these toxicities was related to carboplatin pharmacokinetics.

**Discussion**

The present prospective study was undertaken in order to provide information about drug exposure variability when combining low-dose carboplatin (50 mg/m²/day) with radiotherapy in a radio-chemosensitization strategy. Variability linked to the subject and variability linked to repeated treatment were both examined. A limited sampling strategy based on Bayesian analysis was adopted in order to obtain acceptable and feasible blood sampling over a large pharmacokinetic follow-up (143 cycles in total). The applicability of a Bayesian strategy as presently used for the prediction of carboplatin exposure by use of one of two samples has been previously reported by other investigators [20, 21]. In the present study, we found the AUC values obtained by limited sampling strategy (blood sampling at 1 and 4 h after the carboplatin infusion) to be comparable to those determined with a classical method of extensive sampling (five blood samples per cycle). The absolute percentage error was <20% with an accuracy of 10%. In the present study, the combination of a limited two-point strategy with Bayesian analysis thus provided a relatively unbiased and precise estimate of AUC. When applying this pharmacokinetic follow-up to the whole analysis of 143 cycles it was found that carboplatin AUC exhibited a wide variability with values ranging from 0.360 to 4.200 mg·min·ml, corresponding to CL values from 19.1 to 244.7 ml/min. A component variance analysis of AUC values showed that treatment duration was responsible for <1% of the total variance, while interpatient variability contributed to 68.6%. This time-stability of carboplatin pharmacokinetics may be attributable to the low-dose protocol and the general low nephrotoxicity of carboplatin. The present data concord well with previous results reported in adults [22], but contrast with a decline in CL previously noted in children of 1–4 years of age from courses 1 to 4 of therapy [23]. We examined whether the marked interpatient variability in drug exposure was related to pharmacodynamics and found no obvious pharmacodynamic–pharmacokinetic relationships. This latter observation can be explained by the fact that carboplatin was used in the present protocol as a radiosensitizer; thus the pharmacodynamic manifestations are not directly attributable to the drug effects on the target tissue but rather to the interaction between drug and irradiation at the cellular level. Although there were no direct relationships between treatment side-effects and carboplatin AUC, the high interpatient variability in drug exposure (>10-fold) may suggest differences in the drug-induced radiosensitization. It is thus advisable to limit this variability. Moreover, the use of dose calculation formulas based on individual characteristics is a valuable approach for carboplatin. In the present study, CL was calculated using the Chatelut model which was established for conventional carboplatin dosages [5]. Correlation was reported between observed CLs and values predicted according to the Chatelut formula, indicating that variability in renal function was largely responsible for interpatient variability in carboplatin pharmacokinetics. However, intra-individual analysis of the bias showed that the Chatelut formula overestimated CL by 40% on average. A strong correlation was demonstrated between bias and observed CL: the lower the observed CL the greater the bias (Figure 3). This non-applicability of the Chatelut formula and the
present setting of low carboplatin doses is of practical importance since the challenging carboplatin formula developed by Calvert et al. [4], if applicable in this low-dose situation, would be more cumbersome, in practise, than the Chatelut formula, since it requires the determination of $^{51}$$\text{Cr}$-EDTA clearance. A previous retrospective study by Sculier et al. [24], based on a large number of patients, demonstrated an excellent concordance between the carboplatin AUC values provided by both formulae, even for moderate doses. The non-applicability of the Chatelut formula in the present study of low-dose carboplatin calls for an explanation. The fact that head and neck cancer patients (study patients) frequently exhibit a marked weight loss may help explain the lack of applicability of the Chatelut formula in the present setting. Indeed, serum creatinine level is taken into account when estimating renal function. Creatinine basal levels are linked to muscle mass and thus patients with marked weight loss may exhibit low creatinine due not to high CC but to low basal production of creatinine from muscles. Mazumbar et al. [8] have already pointed out a similar non-applicability of carboplatin dose calculation formula for carboplatin doses outside the usual range. In the absence of a linear model between target AUC and measured AUC (as in the present study) the authors suggested a new model of applicability of the Chatelut formula in the present setting of low-dose carboplatin. The fact that head and neck cancer patients (study patients) calls for an explanation. The non-applicability of the Chatelut formula in the present study of low-dose carboplatin would be more evident if applicable in this low-dose situation, would be more cumbersome, in practise, than the Chatelut formula, since it requires the determination of $^{51}$$\text{Cr}$-EDTA clearance. A previous retrospective study by Sculier et al. [24], based on a large number of patients, demonstrated an excellent concordance between the carboplatin AUC values provided by both formulae, even for moderate doses. The non-applicability of the Chatelut formula in the present study of low-dose carboplatin calls for an explanation. The fact that head and neck cancer patients (study patients) frequently exhibit a marked weight loss may help explain the lack of applicability of the Chatelut formula in the present setting. Indeed, serum creatinine level is taken into account when estimating renal function. Creatinine basal levels are linked to muscle mass and thus patients with marked weight loss may exhibit low creatinine due not to high CC but to low basal production of creatinine from muscles. Mazumbar et al. [8] have already pointed out a similar non-applicability of carboplatin dose calculation formula for carboplatin doses outside the usual range. In the absence of a linear model between target AUC and measured AUC (as in the present study) the authors suggested a new model of applicability of the Chatelut formula in the present setting of low-dose carboplatin.

References


