Intraperitoneal clearance as a potential biomarker of cisplatin after intraperitoneal perioperative chemotherapy: a population pharmacokinetic study

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BACKGROUND: Intraperitoneal (IP) perioperative chemotherapy with cisplatin is an interesting option in ovarian cancer treatment. A combination of cisplatin with IP epinephrine (already shown to improve IP and decrease systemic platinum (Pt) exposure) was evaluated using a population pharmacokinetic analysis.

METHODS: Data from 55 patients treated with cisplatin-based IP perioperative chemotherapy with (n = 26) or without (n = 29) epinephrine were analysed using NONMEM.

RESULTS: Epinephrine halves clearance between peritoneum and serum (IPCL) and increases the Pt central volume of distribution, IP exposure and penetration in tissue. IPCL has a better predictive value than any other parameter with respect to renal toxicity.

CONCLUSION: This confirms that IPCL could be useful in assessing renal toxicity. As IPCL is also linked to tissue penetration and IP exposure, it may be proposed as biomarker. In addition to a Bayesian estimation, we propose a single-sample calculation-way to assess it. Prospective studies are needed to validate IPCL as a biomarker in this context.

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Ovarian cancer is the main gynaecologic cause of death in Western countries, with >75% of diagnosed cases presenting with regional or metastatic disease and a 5-year overall survival rate of approximately 30% (Goodman et al., 2003). The American Cancer Society estimated that 21 550 new cases of ovarian cancer were diagnosed and 14 600 women died of the disease in 2009 in the United States (Jemal et al., 2009).

The standard treatment for advanced ovarian cancer combines optimal cytoreductive surgery (CRS), with intravenous carboplatin–paclitaxel chemotherapy (Aebi and Castiglione, 2008). However, intraperitoneal (IP) chemotherapy (IPC) may be proposed as an additional strategy aimed at achieving a high and more effective cytotoxic local concentration, while decreasing serum concentration (Markman and Walker, 2006). Three randomised phase-III clinical trials show a significant overall and/or progression-free survival advantage when IPC was used after CRS compared with standard doses of intravenous chemotherapy (Alberts et al., 1996; Markman et al., 2001; Armstrong et al., 2006).

The difficulty of the drug to penetrate into the tumour and toxicities linked to high systemic concentrations impede the use of IPC as a ‘routine’ technique (Dedrick and Flessner, 1997; Rowan, 2009). Co-administration of epinephrine and cisplatin (CDDP) was proposed to solve these problems. Indeed, IP administration of this potent vasoconstrictor increased the penetration of platinum (Pt) derivatives into tumours (Duvillard et al., 1999; Favoulet et al., 2001; Chauffert et al., 2003). Such interesting properties led to phase-I studies to assess the feasibility of the IP epinephrine–cisplatin combination in patients with advanced peritoneal carcinomatosis (Moluccon-Chabrot et al., 2006; Guardiola et al., 2010). In particular, Guardiola et al. (2010) showed that IP epinephrine decreases Pt concentrations in serum and is accompanied by a dramatic reduction in renal toxicity. The purpose of this study was to develop a population pharmacokinetic (POP PK) model of CDDP after perioperative IP administration with epinephrine aiming to assess its impact on the PK parameters and look at the phenomena occurring during this chemotherapy from a different angle. As the addition of IP epinephrine also reduces the rate of renal toxicity, a potential link between PK
parameters and the clinical adverse effect of this drug should be investigated.

MATERIALS AND METHODS

Clinical studies and patients

The clinical and PK data used in the analysis were obtained from 55 patients treated with perioperative IPC (PIPC) with \( n = 26 \) or without \( n = 29 \) epinephrine (Guardiola et al., 2009, 2010). Eligible criterion was recurrent epithelial ovarian cancer, with progression at least 6 months after first-line i.v. chemotherapy based on Pt-containing regimen. Inclusion criteria included: histologically documented recurrent epithelial ovarian cancer confined to the peritoneal cavity (no extra-peritoneal disease), possibility of an optimal CRS aiming to remove all tumour nodules, age over 18, WHO performance status 0 or 1, life expectancy \( \geq 3 \) months, and normal haematological, renal and hepatic functions. Owing to the anticipated cardiovascular effects of epinephrine, patients with a history of cardiac pathology were excluded. The study was conducted in compliance with the Declaration of Helsinki and signed informed consent forms were obtained from all patients.

Treatments

The treatment scheme included 4–8 cycles of i.v. induction chemotherapy with paclitaxel (175 mg m\(^{-2}\)) and carboplatin (AUC 5), followed by optimal CRS during which PIPC with CDDP alone or the CDDP–epinephrine combination was administered. Perioperative IPC was administered as previously described (Royer et al., 2009; Guardiola et al., 2010). Epinephrine was then administered at \( t = 1 \) (\( n = 11 \)), \( t = 2 \) (\( n = 12 \)) and \( t = 3 \) (\( n = 3 \)) mg l\(^{-1}\) doses. The CDDP-containing baths lasted 1 h, but for some patients \( n = 11 \) treated with epinephrine, this duration was shortened by 15 min. Indeed, after evaluating the IP Pt concentration, and as these concentrations were low and below the desired threshold (Royer et al., 2010, 2008), this decision (among others) was taken in an attempt to make this lengthy surgical procedure shorter. Three litres of normal saline, 2.2\,\text{mm}\text{Ca}^{2+}\text{glucuronate}, 1 g l\(^{-1}\) Mg\(^{2+}\), 2 g l\(^{-1}\) KCl and 3 g l\(^{-1}\) NaCl were concomitantly intravenously administered for renal toxicity prevention.

Pharmacokinetic study

Peritoneal and blood sampling for PK analysis was as follows: peritoneal and blood samples were taken 1, 30 and 59 min after the beginning of each of the two 1-h baths (5, 25 and 44 min for the 45-min baths). Additional blood samples were collected 4, 6, 8, 16 and 24 h after the PIPC. The samples obtained 16 h after the beginning of chemotherapy were discarded for the last 11 patients because they were inconvenient and not informative (sampling time around 0300 hours). Blood and peritoneal samples were immediately centrifuged and separated in total and ultrafiltered (UF) fractions, then frozen until analysis using a validated method based on flameless atomic absorption spectrophotometry using a Varian SpectrAA 220Z graphite furnace spectrometer with Zeeman effect (Varian, Mulgrave, Australia).

Population pharmacokinetic analysis

Concentration-time data were analysed using the non-linear mixed-effects approach with the NONMEM program version VI.2 software, with double precision (ICON Development Solutions, Elliott City, MD, USA) (Beal et al., 1989–2006). The first-order conditional method with the INTERACTION option was used. Both UF and protein-bound Pt (\( \text{PtB} = \text{total Pt} - \text{UF Pt} \)) were modelled simultaneously using the following (for details, see Supplementary data S1):

\[
\text{PtB} = \frac{V_{\text{max}} \times \text{Pt UF}}{K_{\text{M}} + \text{Prot}}
\]

This formula was used to model \( \text{PtB} \) following the model of Urien and Lokie (2004). The \( \text{PtB} \) was modelled as an additional compartment and underwent first-order elimination from this compartment (Figure 1). This model was only applied to the serum concentrations because IP Pt binding was shown to be very low (Royer et al., 2005, 2008).

Identification of the best structural PK model was based on the objective function value and on the inspection of diagnostic graphs using the Perl speaks NONMEM (PsN) (Lindbom et al., 2005) and Xpose4 (Jonsson and Karlsson, 1999) toolkits. These programmes were also used to compute the extent of shrinkage in empirical Bayes estimates (eta-shrinkage) and individual predictions (epsilon-shrinkage). Computations were performed in the supercomputer facilities of the Mésocentre de calcul de Franche Comté.

Interindividual variability (IVI) was modelled exponentially. Several error models (i.e., additive, exponential or the combination of both error models) were investigated to describe the residual error. The covariates tested were age, actual body weight, height, body surface area (BSA) calculated according to the Du Bois and Du Bois formula (Du Bois and Du Bois, 1916), body mass index, serum creatinine, creatinine clearance (calculated according to the Cockroft–Gault equation (Cockroft and Gault, 1976)), IP total protein concentration (PRIP), serum total protein concentration (PROT), and presence of epinephrine (EPI – dichotomously coded because Pt plasma concentrations were similar regardless of the dose used (Guardiola et al., 2010)). Only covariates with a biologically plausible effect were tested. A covariate was retained in the population model if it produced a decrease in the objective function value of at least 3.84 points compared with the structural PK model, led to a reduction in the IVI of the associated PK parameter, and if a minimum increase in \( 7 \) was observed after its removal from the final model.

Model evaluation

The accuracy and robustness of the final population models were assessed by a (nonparametric) bootstrap method (Green and
Duffull, 2003), visual predictive check and normalised prediction distribution errors (Brendel et al, 2006; Comets et al, 2008).

Assessment of the epinephrine effect on Pt transfer
To evaluate to what extent epinephrine reduces the amount of Pt transferring from peritoneum to bloodstream, we assessed such an individual transfer rate (RT) as follows (for details, see Supplementary data S1):

\[ RT = \frac{AMT_{\text{serum}}}{AMT_{\text{IP}}} \times 100 \]

(\( RT \), percentage of Pt, which passed from the peritoneum cavity to the bloodstream, AMT serum, amount of Pt in serum, AMT IP, amount of IP Pt).

Pt penetration distance assessment
An individual assessment of the distance at which the interstitial Pt concentration is 5% of that of the IP interface (named 3x0), that is, an estimation of the Pt penetration, was determined following the studies of Dedrick and Flessner (1997) (for details, see Supplementary data S1):

\[ 3x_0 = \frac{3D \times \text{BSA}}{\text{IPCL}} \]

With 3x0 (\( \mu \)m), BSA (\( \mu \)m²), D diffusivity (\( \mu \)m² min⁻¹) (obtained from El-Kareh and Secomb (2004)) and IPCL is the individual clearance obtained with the Uf model (\( \mu \)m min⁻¹).

Length of IP Pt exposure
The time during which the IP concentration was over 10 mg l⁻¹ was calculated as follows using an equation derived from Kuti et al (2004):

\[ T = \ln \left( \frac{AMT_{\text{IP}}}{IPV \times 10} \right) \times \text{IPV} / \text{IPCL} \]

(\( T \), time at which the 10 mg l⁻¹ concentration is reached in the peritoneum, AMT IP and IPV as previously described, IPV, individual volume of distribution associated with the IP compartment).

Assessment of predictive value of PK parameters regarding renal toxicity
As postoperative renal toxicity remains the main adverse effect of PIPC (Guardiola et al, 2009; Pili-Floury et al, 2011), and as epinephrine dramatically reduces the occurrence of such toxicity, we assessed a potential link between several PK parameters (IPCL, CL, AUC serum and AUC IP) and this toxicity. Renal toxicity was assessed according to RIFLE classification based on postoperative serum creatinine level changes from baseline (for details, see Supplementary data S1). Receiver operating characteristics curves were then calculated for each PK parameter. This allowed us to determine a threshold that was used to assess sensitivity, specificity, positive predictive value, negative predictive value and the odds ratio for each PK parameter.

RESULTS
Patient population and structural PK model
Clinical data of the patient population are summarised in Table 1. A total of 316 IP samples and 577 Uf plasma and 577 bound samples were used for the analysis. A three-compartment model with first-order elimination from the central compartment best fitted the data of all patients (Figure 1). The corresponding PK parameters were IPCL, volume of distribution associated with the IP compartment (IPV), clearance from the serum (central) compartment (CL), volume of distribution associated with the serum central compartment (V), Michaelis–Menten constants used to model covalent binding to protein (\( V_{\text{max}} \) and \( K_{\text{m}} \)), elimination constant rate of Pt (\( k_b \)), and the rate constants between serum central and peripheral compartments (\( k_{32} \) and \( k_{23} \)) (Table 2). Interindividual variability on \( k_{32} \), \( k_{23} \), \( K_{\text{m}} \) and \( k_b \) could not be estimated. A correlation between V and \( V_{\text{max}} \) was observed and estimated. The error model includes both proportional and additive models, but the latter was only applied to IP concentrations.

Covariates
Only epinephrine led to a significant decrease in IIV. Epinephrine decreased the objective functional value and IIV for both IPCL and V. The administration of epinephrine led to an IPCL decrease in 53.1% and an increase in V of 80.5%. Associated variability was reduced by 48.9 and 53.4%.

Model evaluation
The goodness-of-fit plots for all samples of the final model are shown in Figures 2A–D. The goodness was confirmed for each studied compartment (Supplementary Figures S2 – supplementary material). The bootstrapped mean and 95CI of the parameter estimates are summarised in Table 2.

The figures corresponding to the posterior visual predictive check and the normalised prediction distribution errors evaluation confirm the satisfactory predictability of the final population PK models (Supplementary material – Supplementary Figures S3A and S3B, respectively). In particular, the 15-min reduction of PIPC was correctly modelled (see Supplementary Figure S3A) and thus

Table 1 Summary of baseline characteristics of patients who underwent IP peroperative chemotherapy with CDDP combined or not with epinephrine

| Parameter          | IP CDDP (n = 29) | IP CDDP – epinephrine association (n = 26) | All patients (n = 55) |
|--------------------|------------------|------------------------------------------|-----------------------|
| Age (years)        | 58.2 (25.5–75.0) | 59.1 (26.6–70.8)                         | 58.3 (25.5–75.0)      |
| Actual weight (kg) | 57 (49–84)       | 61 (49–85)                               | 60.5 (49–85)          |
| Lean body mass (kg)| 43.0 (38.4–56.2)| 43.8 (36.6–51.7)                         | 43.6 (36.6–56.2)      |
| Height (cm)        | 163 (150–176)    | 160 (150–178)                            | 161.5 (150–178)       |
| Body mass index (kg.m⁻²) | 23.6 (17.9–28.5) | 23.4 (20.2–31.2)                         | 23.4 (17.9–31.2)      |
| Body surface area (m²) | 1.26 (1.48–2.01) | 1.63 (1.42–1.92)                         | 1.63 (1.42–2.01)      |
| Lean body mass (kg) | 44.7 (38.4–56.2)| 44.5 (36.6–51.7)                         | 44.7 (36.6–56.2)      |
| Serum creatinine (µmol.l⁻¹) | 57.1 (32–79)    | 62.5 (48–88)                             | 58.0 (32–88)          |
| Creatinine clearance (ml.min⁻¹.m⁻²) | 80.0 (58.2–133.2)| 94.0 (58.2–142.8)                        |                       |
| Total protein concentration in serum (g.l⁻¹) | 31.0 (16–42)    | 36.5 (22–56)                             | 34.0 (16–56)          |

Abbreviations: CDDP = cisplatin; IP = intraperitoneal. *Calculated according to the Dubois and Dubois formula. †Calculated according to the James formula. *Estimated with the Cockcroft and Gault formula. Data are presented as median (range).
enables us to analyse these patients together with those treated with the 1-h baths.

Impact of epinephrine effect on Pt

The decrease in IPCL because of epinephrine reduced the rate of transfer of Pt from peritoneum to bloodstream by 40.2% (mean individual, $P<10^{-5}$) (Figure 3A). This was accompanied by an increase in the length of time during which Pt concentration was higher than 10 mg l$^{-1}$ (a concentration associated with the increase in the length of time during which IP Pt concentration was also led to an increase in the calculated Pt penetration in tissues increases together with the rate and extent of Pt transfer outside the capillaries, resulting in lower total Pt serum concentration (Fagioliino et al., 2006). Of note, an increase in V was also observed when epinephrine was used in combination with local anaesthetics after perineural administration (Tucker and Mather, 1979) meaning that this effect is probably not related to the mode of administration, nor to the combined drug. The decrease in IPCL is thought to be partly due to a reduction in splanchnic blood flow ($\alpha_1$-adrenergic vasodilatation) and a $\beta_2$-mediated peripheral vasodilatation (decrease in peripheral resistance). Consequently, the blood flow distribution in tissues increases together with the rate of transfer of Pt from peritoneum to bloodstream by 40.2% (mean individual, $P<10^{-5}$) (Figure 3A). This was accompanied by an increase in the length of time during which Pt concentration was higher than 10 mg l$^{-1}$ (a concentration associated with the cytotoxicity of a resistant cell line (Royer et al., 2005; Macy et al., 2011)). After epinephrine administration, this duration more than doubled (25.1 ± 6.8 min vs 53.9 ± 13.5 min, $P<10^{-4}$) (Figure 3C). Interestingly, the addition of epinephrine in the peritoneal bath also led to an increase in the calculated Pt penetration in interstitial tissue. The mean Pt penetration was 992 ± 219 µm without epinephrine vs 2100 ± 473 µm with epinephrine ($P<10^{-4}$) (Figure 3B).

Selection of IPCL as the best marker of toxicity

Of the 29 patients who did not receive epinephrine, 28 were able to undergo renal toxicity assessment (Supplementary data S1). Of these, 14 underwent high clinical toxicity (IP) while this toxicity was lower in the 14 other patients. The 26 patients treated with epinephrine did not develop renal injury or failure.

Receiver operating characteristics curves indicate that IPCL, AUCIP, and AUCserum, but not CL are able to discriminate patients with a potential risk of renal toxicity (Supplementary data – Supplementary Figure S4). For these three PK parameters, predictive values (sensitivity, specificity, positive predictive value, negative predictive value and odds ratio) show that IPCL seems to be the best parameter for predicting potential CDDP toxicity (Table 3). To reduce the number of samples and simplify the sampling schedule, the Bayesian estimation of IPCL was assessed with only the last IP sample of each bath. These estimations led to satisfactory values of IPCL with a higher positive predictive value than IPCL obtained with all samples, but a lower negative predictive value (Table 3 and Supplementary data – Supplementary Figure S4). However, a biomarker must be easily accessible in order to be effective. We therefore aimed to calculate IPCL directly using the UF IP concentration of Pt with the following formula:

$$\text{IPCL} = -\frac{V}{T} \ln \left( \frac{C(t) \cdot V}{D} \right)$$

(1, volume in which Pt is administered with the dose $D$ (mg); $C(t)$, concentration of UF IP Pt measured at the time $t$).

Taking the last values of Pt of each bath, the calculated IPCL values give a lower AUC for receiver operating characteristics curve (Supplementary data – Supplementary Figure S4), but provide good predictive values that are similar to those observed with the Bayesian estimation or with all the samples (Table 3).

**DISCUSSION**

Population pharmacokinetic studies give another view of the pharmacokinetic phenomena taking place during this chemotherapy. We described the effect of epinephrine on V and on the clearance between IP and serum. The considerable increase in V after epinephrine administration was somewhat surprising. The role of epinephrine in the increase in V may be explained by a $\beta_1$-adrenergic-mediated myocardial stimulation (positive inotropic and chronotropic actions) and a $\beta_2$-mediated peripheral vasodilatation (decrease in peripheral resistance). Consequently, the blood flow distribution in tissues increases together with the rate of transfer of Pt from peritoneum to bloodstream by 40.2% (mean individual, $P<10^{-5}$) (Figure 3A). This was accompanied by an increase in the length of time during which Pt concentration was higher than 10 mg l$^{-1}$ (a concentration associated with the cytotoxicity of a resistant cell line (Royer et al., 2005; Macy et al., 2011)). After epinephrine administration, this duration more than doubled (25.1 ± 6.8 min vs 53.9 ± 13.5 min, $P<10^{-4}$) (Figure 3C). Interestingly, the addition of epinephrine in the peritoneal bath also led to an increase in the calculated Pt penetration in interstitial tissue. The mean Pt penetration was 992 ± 219 µm without epinephrine vs 2100 ± 473 µm with epinephrine ($P<10^{-4}$) (Figure 3B).

### Table 2 Population pharmacokinetics parameters of Pt estimated from the final model and bootstrap validation (500 resamplings)

| Parameter | Original data (mean (%RSE)) | Bootstrap analysis (mean (%RSE)) | Shrinkage (%) |
|-----------|----------------------------|---------------------------------|--------------|
| Structural model | IPV (I) | 3.10 (3.1) | 3.11 | 2.94 to 3.26 |
| IIVBmax (%CV) | 51.3 (12.2) | 50.8 | 44.6 to 56.9 | 0.7 |
| IIVCL (%CV) | 39.4 (28.2) | 38.0 | 30.1 to 47.3 | 9.1 |
| IIVV (%CV) | 26.4 (42.5) | 26.5 | 17.0 to 38.1 | 6.8 |

### Table 3 Summary of the main population parameters, summary statistics and comparison between samples (mean (95% CI))

| Parameter | Summary | Comparison |
|-----------|---------|------------|
| $t_1$ (h) | 4.66 (4.3) | 4.66 (4.3) |
| $t_2$ (h) | 0.0123 (9.2) | 0.0124 (9.2) |
| $k_{o2}$ (mg l$^{-1}$) | 0.98 (0.7) | 0.98 (0.7) |
| $k_{o1}$ (mg l$^{-1}$) | 0.124 (29.3) | 0.123 (29.3) |
| $k_{o3}$ (mg l$^{-1}$) | 0.101 (9.1) | 0.105 (9.1) |

### Table 4 Comparison of the mean AUC and IPCL values for inflammatory and non-inflammatory samples (mean (95% CI))

| Parameter | Inflammatory | Non-inflammatory | Comparison |
|-----------|--------------|-----------------|------------|
| IPCL (µmol) | 13.5 min | 13.5 min | 0.02 (0.00) |

**Abbreviations**: $\theta$: parameter of the value associated with the equation of the covariate; $y$: exponential part of the residual error; $\alpha$: additive part of the residual error; CI: confidence interval; %CV: percentage of coefficient of variation; CL: clearance associated with the serum (central) compartment; IPCL = IP clearance; IIV = interindividual variability; Pt = platinum; %RSE = relative standard error; V and IPV = volume of distribution associated with the serum central and IP compartments; $V_{max}$ and $K_{MM}$ = the Michaelis-Menten constants used to model covalent binding to protein; $k_{o}$ = the elimination constant rate of Pt-bound Pt to protein; $k_{o2}$ and $k_{o3}$ = rate constants between central and peripheral compartments.
Figure 2. Scatterplots allowing us to assess the goodness-of-fit for the final models. Graphs represent model-Predicted (PRED) (A) and Individual Predicted (B – shrinkage ≤ 1.0%) concentrations plotted vs Observed concentrations, as well as Conditional (C) and Individual (D) Weighted Residuals vs Time. These concentrations were observed for the concentrations obtained IP, in serum and for bound Pt. The scatterplots for each compartment are displayed in Supplementary Figure S2 of the Supplementary data.

Figure 3. Effect of epinephrine on Pt behaviour during PIPC. (A) The effect of epinephrine on individual rate of transfer of Uf Pt from peritoneum to bloodstream. (B) Assessment of the effect of epinephrine on the individual Pt penetration. $3\sigma_0$ (µm) is the distance in peritoneal tissue at which the concentration difference between tissue and blood perfusing this tissue decreased to 5% of its maximal value. (C) Time during which the IP Pt concentration is over 10 mg l$^{-1}$. The data were obtained for patients treated with cisplatin with (white box) or without (grey box) epinephrine. $\dagger$ means $P < 10^{-3}$ (t-test) as compared with values observed without epinephrine.
time during which the concentration is above 10 mg l⁻¹. These effects are interesting as, to be clinically relevant, the high and sustained IP Pt level must result in significant Pt accumulation in tumour nodules (Rao et al., 2007; Van der Speeten et al., 2009).

The administration of epinephrine led to the suppression of the clinically relevant renal toxicity previously observed in around half of the patients (Supplementary data S1). As we observed that epinephrine administration led to a great difference in both creatinine ratio and serum Pt concentrations (Guardiola et al., 2010), we assumed that, thanks to the POP PK study providing access to individual PK parameters, this could help us to determine a PK parameter linked to renal toxicity. IPCL was the best PK parameter for predicting renal toxicity, showing the best predictive values. This is unsurprising, as this parameter pharmacokinetically drives both the IP and serum AUC. Interestingly, IPCL may also be used to compute pharmacodynamic parameters. However, as we could not directly link this parameter to efficacy, further prospective studies are needed to correlate this parameter with efficacy. This parameter could thus be used to assess both toxicity and possibly efficacy of cisplatin perioperative IP administration. Indeed, there are a few biomarkers in the field of IPC. Although CA125 was proposed as a predictor of progression-free and overall survival in ovarian cancer patients before IPC (Juretzka et al., 2007), its interest is controversial (Juretzka et al., 2011), and both low IP protein concentration and low protein binding leads to this volume being close to V. Thus, considering both the administered dose and volume (easily available with an open procedure), the IP Uf concentration obtained just before the end of IPC can be used to calculate the IPCL directly using the equation previously described. Using this method, we obtained IPCL predictive values similar to those obtained using NONMEM (with the full model or the Bayesian estimation), which makes this parameter easily available even without POP PK modelling (with or without epinephrine). However, the approximations used to calculate this parameter may weaken its predictive value. For instance, the individual estimation of IPCL using the POP PK approach indirectly takes into account parameters that dictate the Pt transfer, such as the permeability and the effective contact area (Supplementary data S1). Direct calculation of IPCL with the proposed formula does not. In the event of huge preoperative malignant ascites, POP PK estimation of IPCL may be more realistic than the calculated approach. The estimation of the surface of the contact area by BSA for the interstitial penetration assessment may also be biased. For these reasons, it seems very important to assess the predictive values of these parameters in prospective studies in which these potential biases should be detected and evaluated.

In conclusion, the present POP PK analysis aimed to propose a potential biomarker of cisplatin after PIPC. Two characteristics of this study make this possible. First, the POP PK approach provides access to individual PK parameters. Second, the administration of epinephrine led to a dramatic reduction in renal toxicity. Taken together, these approaches led to a correlation study, which showed that the IPCL appears the best parameter linked to toxicity, and that this parameter could potentially be related to efficacy. Given that the POP PK approach is not widely available, we propose a more simple approach to assess this parameter. Although the assessment of IPCL with only one sample using the proposed equation is not as precise as the Bayesian estimation, this approach may be universally adopted with a view to a prospective study to confirm this approach and determine an essential threshold for patient follow-up.

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Conflict of interest

The authors declare no conflict of interest.

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