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ORIGINAL ARTICLE

Improvement in intraperitoneal intraoperative cisplatin exposure based on pharmacokinetic analysis in patients with ovarian cancer

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Abstract Ovarian cancer is the leading cause of gynecological cancer-related death in Western countries. The present treatment standards for ovarian cancer are based on the association of debulking surgery with platinum-based chemotherapy. Another strategy that could be further investigated is intraperitoneal chemotherapy (IP). We previously described that the 2-h administration of intraoperative IP cisplatin did not reach satisfactory concentrations. In the present study, we present the results of a pharmacokinetic analysis performed after two consecutive 1-h IP 30 mg/l cisplatin administrations. Twenty-seven patients with advanced epithelial cancer classified FIGO stage IIIC were included in the study. Blood and IP samples were taken over a 24-h period, during and after IP treatment. Both total and ultrafiltered (Uf) platinum (Pt) concentration levels were analyzed. Biological and clinical toxicities were also recorded. With this strategy, IP Pt concentrations stayed above the target concentration (10 mg/l) for a satisfactory length of time. The serum Pt concentrations were higher than those observed with the "one-bath" protocol and they induced the occurrence of recoverable renal toxicities (3 grade 1, 7 grade 2 and 4 grade 3). The best predictive parameter for renal failure was the total Pt 24-h Area Under the Curve (AUC) with a threshold value of 25 mg h/l RR = 0.31 (95% CI 0.13 − 0.49, $P < 0.01$). Administration of an increased amount of cisplatin is feasible and a satisfactory level of IP Pt concentrations is obtained. However, this improvement is associated with an increase in serum Pt levels and resulting renal toxicities. An attractive solution would be to decrease Pt transfer from peritoneum to bloodstream. A phase 1 study using intraoperative IP epinephrine in order to decrease this transfer is presently being carried out.

Keywords Pharmacokinetic · Cisplatin · Ovarian neoplasms · Intraperitoneal Infusions

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Introduction

Advanced epithelial ovarian cancer is the leading cause of gynecological cancer-related death in Western countries and the fourth most common cause of cancer-related death among women. More than 75% of diagnosed cases present with regional or metastatic disease. The associated 5-year survival is around 30% with III and IV stage disease [10, 11, 17].

The standards for ovarian cancer treatments were initially based on the association of debulking surgery with platinum-based chemotherapy [4, 9]. However, recent data suggest that the combination carboplatin–paclitaxel associated with an aggressive surgical bulk reduction could be a standard first-line treatment [4, 9, 20]. An additional strategy can also be proposed: intraperitoneal chemotherapy. The rationale for administering intraperitoneal (IP) chemotherapy to patients with ovarian cancer and peritoneal involvement is that it has high drug concentration exposure; this leads, however, to increased cytotoxicity and a high level of systemic toxicity [6, 16]. Several multicenter phase III clinical trials have shown a survival benefit [2, 3, 15], and this improvement has been confirmed by a meta-analysis of initial management of primary epithelial ovarian cancer which included eight randomized trials [12].

Intraoperative IP chemotherapy has been suggested as an alternative approach to improve IP treatments. Indeed, one of the reasons suggested for IP chemotherapy treatment failure is inadequate diffusion in the peritoneal cavity, due to adhesion barriers and/or anatomic niches. Administration of chemotherapy during surgery is of interest as the surgeon, who stirs the cisplatin liquid in the peritoneum manually, controls the diffusion and the distribution near the resected areas providing optimal peritoneal cavity exposure. Moreover, along with the associated abdominal pain and systemic toxicities, additional adverse effects occur when an infusion catheter is used for the administration of IP chemotherapy [12, 16, 18]. These complications are common and include catheter obstruction, chemotherapy leakage around the catheter or surrounding subcutaneous tissues, infections, etc. [16]. To deal with these problems, an "open" intraoperative IP administration can be performed after optimal cytoreductive surgery by filling the peritoneal cavity with saline containing chemotherapeutic agents [1, 19]. Even if such method also presents disadvantages such as insufficient exposure of the laparotomy wound and, consequently, existence of small parts of the peritoneum not exposed to chemotherapy leading to potential tumor recurrence, exposure of operation theatre personnel to chemotherapeutic drugs by spilling, direct contact and aerosols, etc [23], this kind of administration eliminates catheter perfusion and related adverse effects and it confers best drug diffusion by manual mixing.

In a previous study using this method, we described the pharmacokinetic parameters of platinum with a 2-h intraoperative IP treatment and established that the IP platin target concentration required for cytotoxicity was 10 mg/l [19]. The pharmacokinetic analysis showed that the platin peritoneal exposure in our study fell below this threshold value within 15 min after the beginning of intraoperative IP chemotherapy administration. Also, patient exposure to platin, expressed as the Area Under the Curve (AUC), after a 50 mg/m^2 intraoperative IP treatment, was similar to an intravenous 100 mg/m^2 administration. These results suggest the use of two consecutive 1-h IP administrations of 30 mg/l of cisplatin instead of improving IP exposure by increasing cisplatin dosage above 50 mg/m^2. For this second study, we preferred to express the cisplatin dosage in "mg/l" to be closer to the desired IP target (10 mg/l). The resulting pharmacokinetic analysis is presented in this study.

Patients and methods

Patients and treatments

Twenty-seven patients with advanced epithelial ovarian cancer classified FIGO stage IIIC were included in the study. Their Performance Scores (WHO) were 0–1 and the median age at the time of diagnosis was 57.9 years (range 35.5–75.0). Tumors were undifferentiated carcinomas in 14 cases, and poorly, moderately and well-differentiated in 8, 4 and 1 cases, respectively. The cell types were mucinous in ten cases, serous in 11 cases, papillary serous in four cases, papillary in one case and endometrioid in one case.

The treatment scheme included 4–8 cycles of intravenous (IV) induction chemotherapy with paclitaxel and carboplatin followed by debulking surgery during which intraoperative intraperitoneal (IP) chemotherapy with cisplatin was administered.

The debulking surgery consisted of optimal cytoreductive surgery removing all visible tumor, after which IP chemotherapy was administered before closure of the laparatomy. Intraoperative IP chemotherapy was performed by filling the peritoneal cavity with 3 l of 37°C-heated isotonic saline containing a total amount of 90 mg of cisplatin (i.e., a concentration of 30 mg/l). Gentle stirring was manually carried out by the surgeon. One hour after the beginning of intraoperative IP chemotherapy, the peritoneal cavity was cleared out, rinsed and refilled with the same solution as the first bath. This second intraperitoneal bath lasted 1 h, after which the peritoneal cavity was cleared out, rinsed and closed up. Concomitant and post-surgical intravenous hydrations with a minimal administration of 3,000 ml of normal saline, 2.2 mM Ca^{2+}, glucuronate, 1 g/l Mg^{2+}, 2 g/l KCl and 3 g/l NaCl were administered to try to prevent renal toxicity.

This study was conducted according to the principles set out in the Declaration of Helsinki and included complete patient information and signed informed consent.

Pharmacokinetic study

Peritoneal sampling was performed 1, 30 and 59 min after the beginning of each of the two baths. Blood samples were

taken at the same time (i.e. 1, 30, 59, 61, 90 and 120), and then 4, 6, 8, 16 and 24 h after the intraoperative IP treatment. Pharmacokinetic samples were centrifuged at 4°C and then divided into two fractions. One was used for total Pt determination and was frozen after centrifugation. The other fraction was ultrafiltered (Amicon Ultra-4, Millipore, Bedford, MA, USA) for determination of ultrafiltered (Uf) platinum (Pt) and was also frozen for measurement. Total protein concentrations were measured in all samples by an automated Biuret method (Dade Behring, Paris La Défense, France). The other biological parameters: serum creatinine, serum electrolytes (including K^+, Na^+, Cl^-, Mg^{2+}), lactate concentrations and blood counts were obtained by routine procedure. The AUCs calculated during the 24-h period and for both compartments were calculated using a trapezoidal method. Total and Uf pharmacokinetic parameters were calculated separately.

Platinum concentration measurements were performed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). A Hewlett Packard (Les Ulis, France) model 4500 ICP-MS was used. The flow of Argon gas was delivered with an outer gas flow-rate of 15 l/min and a nebulizer (Cross flow) flow-rate of 1 l/min. The MS was equipped with a two-cone interface and a quadrupole mass analyzer. The sample uptake rate was 0.2 ml/min. The ions selected from Pt and bismuth (internal standard) were measured at m/z of 195 and 209, respectively. Pt standard solution, bismuth solution and nitric acid were purchased from Merck (Darmstadt, Germany). All chemicals and reagents were of the highest available grade and were used without further purification. The samples were prepared by diluting 50 µl of serum with 4,950 µl of diluent containing 1% nitric acid and 10 µg/l of bismuth (ca. 100-fold dilutions). Calibration curves for Pt were prepared in serum obtained from healthy volunteers, and spiked with standard working solution to cover the concentration range of 0–1,000 µg/l. The standards were diluted 100-fold with the same diluent as the samples before they were placed in the nebulization chamber. The limit of detection, calculated as the mean blank value + three times standard deviation (SD), was 0.01 µg/l. The lower limit of quantification, defined as ten times the SD above the mean blank value, was 0.2 µg/l. The calibration curves exhibited good linearity over the working concentration range of 0–1,000 µg/l. Recovery of Pt added to serum was close to 100% at concentrations of 20 and 200 µg/l. Within-run and between-run coefficients of variation were less than 5% for both concentrations studied.

Toxicity study

The toxicity evaluation was performed via physical examination and routine laboratory tests until the end of the hospitalization. Toxicities were defined according to the National Cancer Institute Common Toxicity Criteria. Renal toxicities were assessed by increase in serum creatinine concentrations and hematological toxicities by assessment of blood counts within 10 days after surgery.

Statistical evaluation

The analysis of the relationship between toxicities and pharmacokinetic parameters was performed using the Chi-square test. The results of the pharmacokinetic parameters are expressed as mean ± standard errors.

Results

Peritoneal pharmacokinetic parameters

The variation in IP Pt concentrations over time is shown in Fig. 1. Uf and total Pt concentrations were similar. The mean maximal values observed were 22.63 ± 8.13 and 23.43 ± 6.99 mg/l for Uf and total Pt, respectively (Table 1). No difference was observed between the two consecutive baths regarding the maximal values or the AUCs. The AUCs calculated for the sum of these two baths were 20.02 ± 6.31 and 24.44 ± 9.13 mg h/l for Uf and total Pt, respectively (Table 1). Interestingly, the time duration with total Pt concentrations over 10 mg/l was 1 h and the time duration with a total Pt concentration over 5 mg/l was almost that of the total duration of the IP procedure.

Serum pharmacokinetic parameters

The variation in serum Pt concentrations over time is described in Fig. 2. This figure shows the two peaks of Pt occurring during the two consecutive administrations of IP cisplatin. These maximal Pt concentrations occurred at 30 and 90 min. The mean maximal values were 1.95 ± 0.41

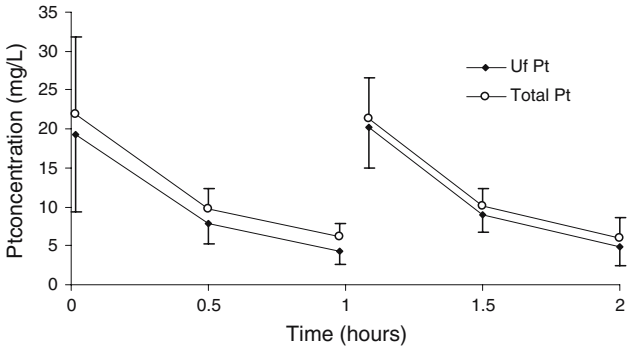

Fig. 1 Evolution over time of IP Pt concentrations. The concentrations were measured during two consecutive 1-h administrations of 90 mg of CDDP diluted in 3 l of isotonic saline. Uf Pt was separated after ultrafiltration. The results are the mean ± SD of 27 patients

Table 1 Comparison of Pt pharmacokinetic parameters observed IP or in serum

		AUCs (mg h/l)	C_{max} (mg/l)
Mean serum Pt pharmacokinetic parameters			
Uf Pt	1 administration	3.72 ± 1.36 (24 h)	1.00 ± 0.38
	2 administrations	5.90 ± 1.21 (24 h)	1.95 ± 0.41
Total Pt	1 administration	16.48 ± 4.62 (24 h)	1.36 ± 0.37
	2 administrations	25.24 ± 5.77 (24 h)	2.70 ± 0.43
Mean intraperitoneal Pt pharmacokinetic parameters			
Uf Pt	1 administration	10.23 ± 2.91 (2 h)	11.67 ± 3.35
	2 administrations	20.02 ± 6.31 (2 h)	22.63 ± 8.13
Total Pt	1 administration	11.73 ± 2.44 (2 h)	12.06 ± 3.04
	2 administrations	24.44 ± 9.13 (2 h)	23.43 ± 6.99

The Pt pharmacokinetic parameters were obtained after two different IP CDDP administration protocols: a protocol with one administration of 50 mg/m^2 CDDP (labeled "1 administration") and a protocol with two consecutive 1-h administrations of 90 mg CDDP each (labeled "2 administrations"). Each administration of CDDP was diluted in 3 l of isotonic saline. The parameters studied were the mean ± SD value of maximal concentration (C_{max}) and the values of IP (2 h) and serum (24 h) AUCs

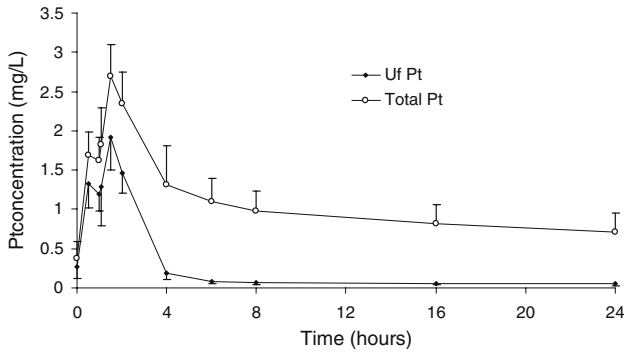

Fig. 2 Evolution over time of serum Pt concentrations. The concentrations were obtained during and after two consecutive 1-h administrations of 90 mg of CDDP diluted in 3 l of isotonic saline. Samples were taken during the 24-h period and Uf Pt was separated after ultrafiltration. The results are the mean ± SD of 27 patients

and 2.70 ± 0.43 mg/l for Uf and total Pt, respectively (Table 1). The difference between total and Uf Pt concentrations varied with time (Fig. 2). The respective AUCs calculated for the 24-h period reflect the same phenomenon. The values observed in Uf and total Pt were 5.90 ± 1.21 and 25.24 ± 5.77 mg h/l, respectively (Table 1). The ratio obtained between serum and peritoneal maximal Uf Pt concentrations was 1/12 whereas the same ratio in Uf Pt AUCs was 1/3. The ratios obtained for total Pt were, respectively, 1/9 for C_{max} and 1/1 for AUCs.

Protein concentrations

Total peritoneal protein concentrations were assessed at the same time as Pt concentrations. As shown in Fig. 3a, the peritoneal protein concentrations increased over time. However, the concentration values were higher during the first bath than those observed during the second bath. This was probably due to the washing of the peritoneal cavity before the second bath. The level of serum protein concentrations remained constant during intraoperative IP chemotherapy (see Fig. 3b). The concentrations were around 30 g/l during surgery and steadily increased afterwards, reaching 40 g/l at 24 h.

Toxicity evaluation

Excepted renal toxicities, none of the usually reported toxicities (abdominal pain, nausea/vomiting, neurotoxicity, hematotoxicity) were encountered with the present modality of intraoperative IP chemotherapy. Of course, none of the toxicities related to drugs delivery through IP catheter were observed. Only transient renal toxicities were observed: three cases of grade 1, 7 of grade 2 and 4 of grade 3 renal failures occurred within the first 10 days after the treatment. Renal function recovered in all patients after intravenous hydration with normal saline 2.2 mM Ca^{2+}, glucuronate, 1 g/l Mg^{2+}, 2 g/l KCl and 3 g/l NaCl.

Patient distribution for both Uf and total AUCs for the occurrence of renal toxicities is shown in Fig. 4. The 24-h AUC of Uf Pt showed patients who experienced renal toxicities and those who did not. A threshold value was identified at 5.9 mg h/l for the 24-h AUC of Uf Pt: hazard ratio = 0.75 (95% CI 0.27–1.24, $P < 0.05$). The best predictive parameter for renal failure was total Pt 24-h AUC. A threshold value was identified at 25 mg h/l for the 24-h AUC of total Pt: risk ratio = 0.31 (95% CI 0.13–0.49, $P < 0.01$). The other parameters studied were C_{max} for Uf and total Pt; IP AUCs were not significant for renal toxicity occurrence.

Discussion

In a previous study, a clonogenic assay determined the peritoneal concentration associated with total cytotoxicity on ovarian cancer-resistant cells (OVCAR-3) [19]. Incubation of 10 mg/l of CDDP for 2 h was associated with a complete inhibition of cell growth. Incubation of 5 mg/l of CDDP for 2 h inhibited cell survival by 90%. With the 10 mg/l threshold, the analysis of Pt pharmacokinetic parameters after 2 h of intraoperative peritoneal treatment using 50 mg/m^2 of CDDP, established that the exposure of the peritoneal cavity cells to Pt was insufficient [19].

Based on these results, we modified the treatment process and two consecutive 1-h administrations of CDDP were administered to patients. This new protocol greatly improved the peritoneal exposure to Pt. The time duration

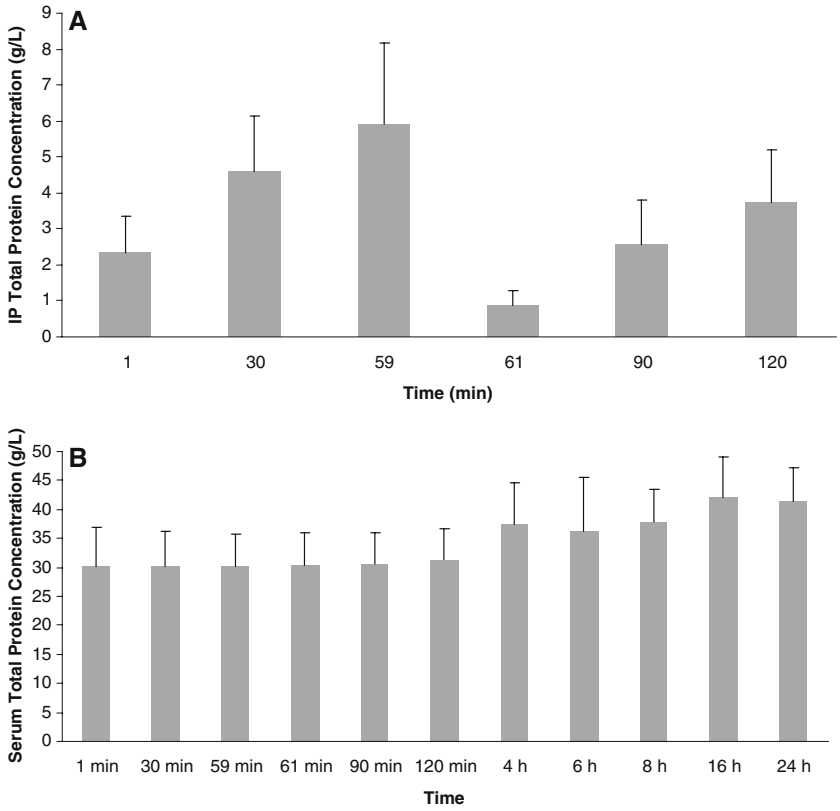

Fig. 3 Evolution over time of the intraperitoneal (**a**) and intravenous (**b**) total protein concentrations. The concentrations were measured with the same protocol as that performed with Pt concentrations and sampled intraperitoneally (**a**) and intravenously (**b**). The CDDP was administered after two consecutive 1-h administrations of 90 mg of CDDP diluted in 3 l of isotonic saline. The results are the mean + SD of 27 patients

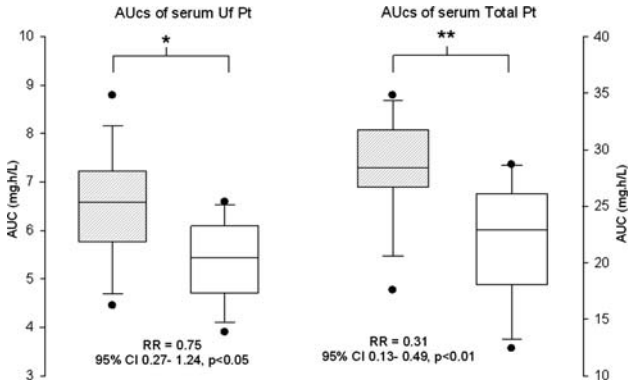

Fig. 4 Distribution of patients with and without renal toxicity. The Uf and total AUC parameters observed in serum are shown for patients who experienced renal toxicity (*hatched boxes*) and those who did not (*blank boxes*). The results are expressed as the median (*horizontal lines in the boxes*) and the 10th (*upper "whisker"*), 25th (*top of the boxes*), 75th (*down of the boxes*) and 90th (*lower "whisker"*) percentiles; *dark filled circle* represents the outliers. *Asterisk* and *double asterisk* express statistical differences with $P < 0.05$ and $P < 0.01$, respectively, for the Chi-square

with a peritoneal Pt concentration above 10 mg/l was more than 1 h and the time duration with a concentration above 5 mg/l was almost 2 h.

Another possibility could be to simply add cisplatin in the peritoneum without replacing the bath by a new one. Such method allowed van Ruth et al. to increase maximal tolerable total dose by approximately three times higher than that of usual method [22]. However, even if such method seems to be more practicable, we preferred to replace the bath 1 h after the beginning of the chemotherapy. Indeed, our previous study has shown an important interindividual variability which leaded to high IP concentrations with some patients [19]. Adding cisplatin in the same bath may lead to very high IP and IV Pt concentrations to these patients. We thus preferred two controlled-concentration administrations of cisplatin.

Both peritoneal and serum concentrations were higher with two cisplatin baths than with one bath. As demonstrated in Table 1, the mean AUCs and maximal peritoneal concentrations were clearly higher with the two-bath protocol. The present study was conducted with a selected double dose as compared to the previous protocol (but administered twice), resulting in a higher exposure than the previous study.

Considering the administered doses, the AUCs of CDDP in the present study are similar to those described by other authors even if such data should be weighted by the doses administered and the perfusion method. Kern et al. described a Uf AUC of 29.27 ± 9.08 mg h/l for IP concentrations and 9.51 ± 0.87 mg h/l for serum concentrations with an IP-administered dose of 150 mg/m^2 [13]. In the study by Cho et al., the authors observed an AUC for total Pt of 75.3 ± 29.2 mg h/l for an IP-administered dose of 300 mg/m^2 [8]. The decrease in the administered doses in our study resulted in logically lower exposure. For IP-administered doses ranging from 50 to 70 mg/m^2, van de

Vaart et al. observed a Uf AUC from 1.44 to 2.19 mg h/l [21] and in our previous protocol, for an IP-administered dose of 50 mg/m^2, we observed a Uf AUC of 3.72 ± 1.36 mg h/l [19].

The dose administered in the present study is lower than that observed in other studies. The present study was carried out with a fixed IP threshold, not with a concentration determined by the body surface area using a maximal tolerate dose obtained after phase I study. This probably explains why we administered lower doses. As well, the ratios between IP and serum concentrations were lower in the present study [5, 6, 14]. Such phenomenon may be linked to the method used: open method and/or lower doses administered versus others studies often performed with hyperthermic intraperitoneal chemotherapy increasing Pt uptake by peritoneal cavity [1, 6, 14, 16].

The increase in Pt concentrations observed in serum was linked to the increased exposure to peritoneal Pt. The shape of the curve of Pt concentrations over time, described in Fig. 2, demonstrates clearly that at each peritoneal administration, a marked increase in serum concentration was observed. In the previous study, we speculated that the protein concentrations might be important for pharmacokinetic parameters of Pt in serum [19]. This observation has been confirmed by the present study as protein levels were also low during IP chemotherapy and remained low afterwards (Fig. 3b). This observation is linked to and explains the differences between Uf and total Pt in serum (Fig. 2). The highest difference was observed 4 h after the beginning of intraoperative IP chemotherapy when both protein and Pt concentrations were concomitantly the lowest and highest respectively.

In our previous study with one bath of 50 mg/m^2, we found that the systemic exposure of patients to Pt was very similar to that observed with a 100 mg/m^2 intravenous protocol [19]. In the present study, a great increase in serum Pt exposure was observed, compared to the one-bath 50 mg/m^2 protocol (Table 1). The serum exposure was above that of the exposure observed after a 100 mg/m^2 CDDP given intravenously and could explain the occurrence of 11 cases with grade 2–3 nephrotoxicities (Fig. 4). All patients recovered from these toxicities. Considering these data, the higher toxicity observed with intraoperative IP chemotherapy performed with a 100 mg/m^2 dose IP as compared to a 75 mg/m^2 comparative intravenous arm pointed out in a recent review is logical [16]. However, it seems important to point out that the only adverse effect observed in our study was renal toxicity. The preoperative administration of platin can thus eliminate catheter infusion and all the related adverse effects [2, 3, 16].

However, this method should not be routinely recommended because of the high rate of renal toxicity. A way to restrict the transfer of Pt from the peritoneum to the bloodstream needs to be found. Our results give additional support to an ongoing phase I study with IP epinephrine and cisplatin. Epinephrine is a vasoconstrictor which has theoretically and experimentally reduced the Pt transfer between peritoneum and bloodstream and increased intratumoral Pt concentrations [6, 7]. The results of our study are expected at the beginning of 2007.

To conclude, intraoperative IP chemotherapy with CDDP is a feasible treatment option for ovarian cancer with peritoneal involvement. In a previous pharmacokinetics study, we observed that intraoperative IP CDDP using 50 mg/m^2 in one bath was insufficient in terms of peritoneal exposure. In the present study, two consecutive intraoperative IP administrations of CDDP at 30 mg/l provided an optimal peritoneal exposure. This improvement induced a significant increase in Pt concentrations in serum and transient nephrotoxicities, which were however, the only adverse effects. To optimize intraoperative IP CDDP, further studies aimed at decreasing the transfer from peritoneum to bloodstream need to be carried out. After the feasibility of IP epinephrine administration was performed [7], a phase 1 study using intraoperative IP epinephrine for this decrease is ongoing.

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