

Heated intra-operative intraperitoneal oxaliplatin plus irinotecan after complete resection of peritoneal carcinomatosis: pharmacokinetics, tissue distribution and tolerance

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Background: The purpose of this study was to report the pharmacokinetics (PK) and tolerance profile of intraoperative intraperitoneal chemo-hyperthermia (IPCH) with oxaliplatin and irinotecan.

Patients and methods: Thirty-nine patients with peritoneal carcinomatosis (PC) of either gastrointestinal or peritoneal origin underwent complete cytoreductive surgery followed by IPCH with a stable dose of oxaliplatin (460 mg/m²), plus one among seven escalating doses of irinotecan (from 300 to 700 mg/m²). IPCH was carried out with the abdomen open, for 30 min at 43°C, with 2 l/m² of a 5% dextrose instillation in a closed continuous circuit. Patients received intravenous leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²) just before IPCH to maximize the effect of oxaliplatin and irinotecan.

Results: Irinotecan concentration in tumoral tissue increased until 400 mg/m² and then remained stable despite dose escalations. It was 16–23 times higher than in non-bathed tissues. Increasing doses of intraperitoneal irinotecan did not modify the PK of intraperitoneal oxaliplatin, and the drug concentration ratio was 17.8 higher in tumoral tissue (bathed) than in non-bathed tissues. The hospital mortality rate was 2.5% and the non-hematological complication rate was 25%. However, grade 3–4 hematological toxicity rate was 58%.

Conclusion: Intraperitoneal heated oxaliplatin (460 mg/m²) plus irinotecan (400 mg/m²) presented an advantageous PK profile and was tolerated by patients, despite a high hematological toxicity rate.

Key words: cytoreductive surgery, hyperthermia, intraperitoneal chemotherapy, irinotecan, oxaliplatin, peritoneal carcinomatosis

A new therapeutic concept [1, 2] has permitted long-term survival of selected patients sustaining peritoneal carcinomatosis (PC) [3–5]. This concept is to treat macroscopic PC with complete cytoreductive surgery and residual microscopic disease with intraperitoneal chemo-hyperthermia (IPCH). Complete cytoreductive surgery is necessary because experimental studies show that drug penetration is limited to a few cell layers (1–2 mm in depth) under the surface of the tumor [6]. This phenomenon is similar for heat [7]. Intraperitoneal chemotherapy must be immediate, avoiding an entrapment of residual tumor cells in the post-operative fibrin adhesions [8, 9]. IPCH leads to high local concentrations of antineoplastic agents and their cytotoxicity is improved by hyperthermia [2, 10]. Recently, a randomized study demonstrated the

superiority of this new combined treatment of colorectal PC when compared to the standard non-aggressive approach [11]. Furthermore, we have currently observed results in survival rates close to those obtained after resection of liver metastases [12], leading us to consider that PC is as potentially curable as other metastatic diseases when resectable.

Most IPCH across the world has been carried out with mitomycin C and/or cisplatin [2–5, 10]. However, these drugs are not very efficient against colorectal and appendiceal tumors, which are the most frequent primaries of PC in our Department. The association of 5-fluorouracil (5-FU) with leucovorin is the basic combination to treat colorectal cancers, but 5-FU is a long-acting drug not potentiated by hyperthermia [13]. Recently, two molecules, oxaliplatin [14] and irinotecan [15], demonstrated a major activity against colorectal tumors and should therefore be interesting to use during IPCH. Furthermore, animal studies revealed some pharmacokinetic advantages and greater efficacy of the intraperitoneal over the intravenous route for these drugs to prevent and treat PC

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[16–18]. Finally, they presented a synergy against cancer cells [19].

In a previous clinical trial, we studied the pharmacokinetics of heated intraperitoneal oxaliplatin. We have shown that 460 mg/m² in 2 l/m² of isotonic 5% dextrose, held *in situ* at 43°C for 30 min, following an intravenous perfusion of 5-FU (400 mg/m²) and folinic acid (20 mg/m²), was well tolerated and pharmacologically interesting [20]. 5-FU is given to potentiate the effects of oxaliplatin [21] and irinotecan [22], but cannot be mixed intraperitoneally with them for reasons of pH incompatibility. Using hypo-osmotic intraperitoneal solutions had no pharmacokinetic advantage, but increased the frequency of intra-abdominal hemorrhage [23]. This scheme resulted in a promising 74% 2-year survival rate for the first 24 patients with colorectal PC [24].

Being conscious that this combined treatment of PC is really a treatment of last resort (and a ‘one-shot deal’), we decided to add irinotecan to oxaliplatin in the peritoneal instillation so that the treatment would be the most efficient possible.

This trial analyzes the pharmacokinetics and tolerance of IPCH using oxaliplatin (460 mg/m²) plus irinotecan (increasing doses from 300 to 700 mg/m²), associated with an intravenous perfusion of 5-FU and leucovorin, immediately after complete resection of PC.

Materials and methods

Patient eligibility

From May 2002 to June 2003, we included 39 patients with preoperatively identified PC in this prospective phase I study. The protocol was reviewed and approved by both our institution’s clinical trial review board and by an independent ethics committee. All patients gave their written informed consent for participation in the study.

There were 13 men and 26 women, of mean age 46.4 ± 9.1 years (median: 46, range: 26–60). The primary tumor’s origins were colorectal adenocarcinoma (*n* = 20), appendix peritoneal pseudomyxoma (*n* = 11), endocrine tumor (*n* = 3), malignant mesothelioma (*n* = 3), and small bowel adenocarcinoma (*n* = 2). All patients, except those presenting a peritoneal pseudomyxoma, were pre-treated during at least 3 months with systemic chemotherapy, because of the waiting list to receive IPCH in our institution. Chemotherapy comprised oxaliplatin- or irinotecan-based regimens for colorectal cancer, gemcitabine plus oxaliplatin for mesothelioma, and adriamycin plus streptozotocin for endocrine tumors.

Surgical procedures

At laparotomy, macroscopic PC was confirmed by frozen section and the extent of disease was scored according to Sugarbaker’s peritoneal cancer index [25]. Macroscopically detectable disease had to be completely resected before including the patient in the trial. Such surgery resulted in a R1 resection. In the case of incompletely resectable PC, we immediately abandoned the operation. Resection of peritoneal surface cancer followed principles previously described [26]. Intestinal anastomoses were delayed until after IPCH to treat bowel margins. There were no temporary stomas. During each procedure, one 5 mm-sized tumor nodule (or 2–3 nodules of 2–3 mm) was marked and left in place during IPCH. We then resected it after IPCH to analyze intratumoral oxaliplatin and irinotecan penetration.

Intraperitoneal chemo-hyperthermia

Before the onset of the study on humans, we ascertained that the mixture of oxaliplatin plus irinotecan was stable *in vitro* in a 5% dextrose solution (pH 5) at 50°C during 4 h (stability testing: atomic absorption spectrophotometry and high-performance thin-layer chromatography (HPTLC) with ultraviolet detection). We then ensured that it was stable *in vivo* in the peritoneal cavity of rats.

We carried out IPCH with a continuous closed circuit using four 36-French drains (two inlets and two outlets) connected to two pumps. We used one heating unit and two heat exchangers to eliminate a Y connector that could reduce flow rates and heat homogeneity [27]. IPCH was carried out with the abdomen open and the skin edges elevated (Coliseum technique). Our earlier studies had demonstrated that this technique was the only one to allow temperature homogeneity and complete spatial diffusion of the chemotherapy solution in the whole peritoneal cavity [27]. Flow rate was 1 l/min for each pump. Four thermal probes inside the peritoneal cavity gave continuous temperature feedback; the entire process was monitored and the data stored in a computer. The intra-abdominal temperature was maintained between 42 and 44°C during IPCH. Perfusion duration was exactly 30 min from the time when optimal temperature (42–44°C) was obtained. Usually, 8–10 min were necessary to reach the target homogeneous temperature, causing the total time for peritoneal perfusion to be approximately 40 min. The total oxaliplatin and irinotecan doses were delivered as a bolus in a 5% dextrose solution at the beginning of the procedure. The volume of 5% dextrose solution was 2 l/m². The same calculations of both volume of solution and doses of oxaliplatin and irinotecan from body surface area resulted in the same drug concentration in all patients. One hour before IPCH, we delivered systemic intravenous leucovorin 20 mg/m² and 5-FU 400 mg/m², because 5-FU potentiates the cytotoxic activity of oxaliplatin and irinotecan [21, 22]. 5-FU was not mixed with oxaliplatin in the peritoneal cavity because of pH incompatibility. Following this systemic perfusion, both tumor and healthy tissues were soaked with 5-FU before the beginning of IPCH. A low dose of 400 mg/m² was chosen to avoid intensifying the aggressiveness of the combination of complete cytoreductive surgery + IPCH. In summary, all patients received a tri-therapy (intravenous 5-FU, and intraperitoneal oxaliplatin and irinotecan).

Experimental design

Oxaliplatin was delivered at a dose of 460 mg/m², which was the recommended dosage defined in our previous trial in humans [20]. Irinotecan was added and its dosage progressively increased in seven successive steps. The first dose level was 300 mg/m² and the following were 350, 400, 450, 500, 600 and 700 mg/m². The first level was chosen according to our expertise concerning *i.p.* pharmacokinetic studies using only one molecule (in which the first level was double the recommended intravenous dose) [20, 23]. In this trial, because three molecules were associated, we decided to begin at a lower dose (*i.e.* 300 instead of 360 mg/m²). Before moving to the next dose level, we had to treat at least three patients at each level without their presenting any severe chemotherapy-related toxicity or unexplained post-operative complication. Should one of these complications occur, two additional patients had to be treated at the same dose level without any incident before escalating to the next step, and only after a multidisciplinary committee had approved its ethical legitimacy. As one postoperative complication (mainly aplasia) occurred in one patient at each dose level, five patients were treated at each of the seven dose levels. However, since the pharmacokinetic samples were not complete in four patients, we had to repeat the study and add four additional patients. Thus, we included a total of 39 patients in this study (35 analyzable for the pharmacokinetics and 39 analyzable for tolerance).

Patients received packed red cell transfusions when the hemoglobin was less than 6.5 g/l (toxicity grade 4 of NCI) and platelet transfusions when less than 50 000/mm³ (toxicity grade 3). Granulocyte colony-stimulating factor (G-CSF) was prophylactically delivered to all patients receiving ≥ 500 mg/m² of irinotecan after having observed a grade 3 (500–1000/mm³) or grade 4 (<500/mm³) neutropenia in all patients receiving 400 and 450 mg/m² of irinotecan.

Oxaliplatin assay by flameless atomic absorption spectrophotometry

Plasma sample preparation. We collected from each patient 14 5-ml heparinized blood samples: just before IPCH, when IPCH started, when IPCH reached 42°C, and then every 10 min during the procedure. Samples were then collected at 15 and 30 min, 1, 2, 6, 12 and 24 h after IPCH. Each sample was immediately centrifuged at +4°C, 3000 rotations per min (rpm) (514 g) during 15 min, and frozen at –20°C. An aliquot of plasma was saved for total platinum determination and another one was ultrafiltered by centrifugation through an Ultrafree Millipore membrane (cut-off 5000 Da) for ultrafilterable platinum determination. The ultrafiltrate was stored at –20°C until analysis.

Peritoneal fluid sample preparation. We collected five 5 ml peritoneal samples from each patient: at the start of the procedure (37°C), at 42°C, and then every 10 min. They were immediately centrifuged at 3000 rpm. (514 g) during 10 min at 4°C and frozen at –20°C.

Tissue sample preparation. We studied three types of solid tissue for each patient: the tumor nodule (only the superficial 2 mm were studied for the 5 mm-sized tumor nodules, but all the nodule when smaller than 3 mm), a 5-cm diameter piece of normal peritoneal tissue treated with IPCH and one piece of parietal muscle, which was not in contact with IPCH. We changed gloves and surgical instruments before resecting the muscle sample.

Platinum determination. We carried out platinum assay using flameless atomic absorption spectrophotometry at 265.9 nm with a Perkin-Elmer AA300 spectrophotometer equipped with an HGA 800 furnace, an AS-72 autosampler and its AA Winlab software. We used Pyrocoated graphite tubes of the same brand. Platinum levels were quantified after preparing calibration curves with atomic platinum. Solid tissue measurements were performed on desiccated tissue, reflecting the actual intracellular drug concentration. Each tissue sample was desiccated to reach constant weight, digested in 65% nitric acid (90–95°C for 96 h) and evaporated to dryness. The solid residue was dissolved in 1 ml of a mixture of Triton X-100 (0.1%) and nitric acid (0.2%).

The four types of liquid samples assayed in homogeneous series were spiked with a set volume of matrix modifier. Appropriate dilutions were programmed in a run including calibration and quality control samples. The analytical run was accepted when the QC samples were found within an interval $\pm 15\%$ around the target value. Results were expressed as platinum concentration in $\mu\text{g/ml}$ for liquid samples or in ng/mg for dry tissues.

Simultaneous determination of CPT-11 and SN 38 by high-performance liquid chromatography (HPLC)

Sampling. Heparinized plasma, peritoneal fluid and tissues samples were aliquotted and stored at –20°C as described above for total platinum determination.

Tissue treatment before extraction. An aliquot of tissue was homogenized in ice-cold Tris–HCl 0.1 M pH 8.1 buffer (20 mg/1 ml) using a Polytron®. The homogenate was centrifuged at +4°C and the supernatant was extracted as plasmas and peritoneal fluids.

Treatment of calibration samples, QC and unknown before extraction. A 100 μl aliquot was spiked with 100 μl of internal standard (I.S.) solution (camptothecin) and adjusted to 1 ml with 0.01 N HCl.

Extraction. One milliliter of the above solution was washed and extracted on a conditioned Bond Elut C18 column. The eluate (1.5 ml of acidic methanol) was evaporated to dryness under a nitrogen stream. The residue was dissolved by 1 ml of mobile phase, centrifuged (514 g during 15 min at 4°C) and transferred into a Chromacol® vial.

Chromatography apparatus. We operate a Beckman Gold® HPLC system composed of a 126 solvent module, a 508 auto sampler and its 32 Karat software. The detection module is a Waters 474 scanning fluorescence detector. The stationary phase is a Nucleosil C18 10 μm 250 \times 4.6 mm column.

Chromatographic conditions. Mobile phase: an acetonitrile/water (36:64) mixture containing potassium phosphate and 1-heptane sulfonic acid was adjusted to pH 4. Chromatographic conditions: Injected volume: 250 μl , flow: 0.7 ml/min, analysis time: 20 min, excitation wavelength: 375 nm, emission wavelength: 425 nm for CPT-11 and 530 nm for SN-38 and I.S. The fluorimeter gain was enhanced after the CPT-11 peak and a new auto-zero was programmed at 10.7 min.

Under these acidic conditions, comparable to the pH of the peritoneal fluid, the physiological equilibrium between the lactone and carboxylic forms is displaced towards the lactone form for both CPT-11 and SN-38. This consideration has no impact on the validity of the analytical method and results.

Results. Unknown results were obtained against the calibration curves obtained simultaneously for CPT-11 (25–1000 ng/ml) and SN-38 (5–100 ng/ml) after treatment with the 32 Karat Software. Three QC levels were incorporated in each run to monitor the dynamic range of the assay. Classically, a run was accepted when the QC results were found within $\pm 15\%$ of the target value (or $\pm 20\%$ for the lower one that monitored a level close to the limit of quantification (LOQ)). CPT-11 was easily dosable inside tissues, but SN-38 concentration was below the LOQ set at 1 ng/ml.

Pharmacokinetics

We used the Micropharm® software to analyze the pharmacokinetics results. Because IPCH is not a standard route of administration, no modeling was available. We used the trapezoid rule to calculate the area under the curve (AUC) for concentration versus time values.

Complications

These were scored on a 0-to-5 scale according to a previously published scoring system concerning postoperative complications [28]. Grade 0 represents cases with no complication. Grade 1 complications are those requiring either no intervention or minor interventions such as oral antibiotics, bowel rest, or basic monitoring. Grade 2 complications are those requiring moderate interventions such intravenous medication (e.g. antibiotics or antiarrhythmics), total parenteral nutrition, prolonged tube feeding, or chest tube insertion. Grade 3 complications are those requiring hospital readmission, surgical intervention, or radiologic intervention. Grade 4 complications are those producing chronic disability, organ resection, or enteric diversion. Grade 5 complications result in death. Grade 1 and 2 complications are grouped as ‘minor’. They were not reported in this paper, except for hematological toxic effects, which, albeit classified as grade 2 complications, needed to be detailed. All grade 3–5 complications (considered as ‘major’) were retained for analysis.

Results

Intraoperative parameters

Mean duration of surgery including IPCH was 8.1 ± 2.4 h (median: 8, range: 4.5–12.2), mean blood loss was 887 ± 626 ml (median: 750, range: 200–3000), and the median

Table 1. Hematological toxicity

Irinotecan (mg/m ²)	No. of patients	Hemoglobin		Granulocytes		Platelets	Total patients
		Grade 4 <6.5 g/l	Grade 3 500–1000/mm ³	Grade 4 <500/mm ³	Grade 3 50 000–10 000/mm ³		
300	5	0	2	2	1	3 (60%)	
350	7	0	0	2	1	2 (29%)	
400	6	2	2	3	1	5 (83%)	
450	5	1	0	3	3	3 (60%)	
500	5 ^a	2	2	1	1	3 (60%)	
600	5	3	2	1	3	3 (60%)	
700	5	1	0	2	2	3 (60%)	
						Total: 22 (58%)	

^aOne patient (the sixth) died at day 5 of a non-hematological complication and was excluded from this analysis. Gradings are defined according to criteria of the NCI. The i.p. oxaliplatin dose was constantly 460 mg/m² and i.p. irinotecan was delivered in escalating doses. Patients systematically received G-CSF from ≥ 500 mg/m² of irinotecan. i.p., intraperitoneal; G-CSF, granulocyte colony stimulating factor.

number of intestinal anastomoses was 2 per patient (range: 0–4). The mean number of resected organs was 4.6 ± 2.1 (median: 5, range: 2–9), seven patients underwent a total colectomy and five a urinary anastomosis or suture. The mean peritoneal index (reflecting the extent of PC) was 16.8 ± 2.2 (median: 16, range: 3–36). In all cases, we carried out a complete macroscopic resection of PC. The intraperitoneal temperature was always maintained between 42 and 44°C for exactly 30 min. We did not abandon any procedure prematurely.

Postoperative complications

There was one hospital mortality (2.5%): on postoperative day 5, during a central venous catheter replacement, the patient presented an epileptic crisis in relation to an air embolism, vomited, and sustained an inhalation pneumonitis resulting in adult respiratory distress syndrome (ARDS) and death 4 days later.

The morbidity rate (complications grade 3–5) was 69%: only 12 patients did not present any postoperative complication. Intra-abdominal complications occurred in 10 (25%) out of 39 patients: intraperitoneal hemorrhage in four, digestive fistula in two, and digestive and urinary fistulas in two, all mandating a reintervention. Percutaneous drainage of an abscess was necessary in five patients. A grade 3 diarrhea (>7 stools/day) occurred in 81% of patients. Extra-abdominal non-hematological complications occurred in eight patients: five pneumonias, four urinary tract infections and three central venous catheter infections. There was no neurotoxicity. Eight patients presented the two types of complications (intra- and extra-abdominal). These complications were not significantly related to the dose level of irinotecan.

Hematological toxicity

A severe aplasia was frequent (58%). We considered only the following toxic effects according to the NCI score: grade 4

(<500/ml) granulocytopenia requiring patients' isolation, grade 3 thrombocytopenia (<50 000/ml) leading systematically to platelet transfusion according to our predefined rules in this trial, and grade 4 anemia (<6.5 g/l) mandating packed red cell transfusions. These hematological toxic effects occurred in 22 patients (Table 1), and resulted in a grade 4 postoperative complication in four of them (as mentioned previously). At the two lowest dose levels (300 and 350 mg/m²), five of the 10 patients presented a severe aplasia and at higher dose levels (≥ 500 mg/m² of irinotecan), aplasias occurred with the same rate despite regular administration of G-CSF. The mean delay for aplasia appearance was postoperative day 7 (range: 3–12). It was 8.7 days for the lower steps of irinotecan (300–450 mg/m²) and 5.2 days for the higher steps (500–700 mg/m²), for a mean duration of 2.7 ± 1.6 days. The hematological toxicity was neither statistically correlated with the increasing dosage of intraperitoneal irinotecan ($P=0.328$), nor the duration of preoperative intravenous chemotherapy ($P=0.473$) (when retrospectively considering three groups of patients: less than 6 months of chemotherapy, between 6 and 12 months, and more than 12 months). On the other hand, hematological toxicity was correlated with an important PC (peritoneal index ≥ 20) ($P=0.017$) and with a long duration of surgery ($P=0.046$), these two parameters being tied ($P=0.01$). The mean hospital stay was 28.1 ± 8.3 days (median: 21, range: 13–103).

Pharmacokinetics of oxaliplatin

The results were similar to those reported previously when oxaliplatin was the sole molecule in the peritoneal instillation [20]: the addition of increasing doses of irinotecan in the peritoneal perfusion did not modify its pharmacokinetics (Figure 1). There was a rapid, constant and exponential decrease in platinum concentration in the peritoneal perfusion during IPCH (Figure 2) and half the drug was absorbed during 40 min of the procedure [20]. In the peripheral blood,

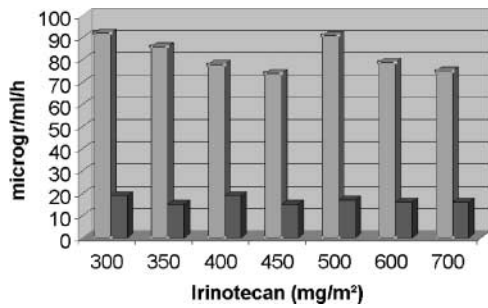


Figure 1. AUC of platinum in plasma for a stable dose of 460 mg/m² of i.p. oxaliplatin and increasing doses of i.p. irinotecan. Total platinum, light grey bars; UF platinum, dark grey bars.

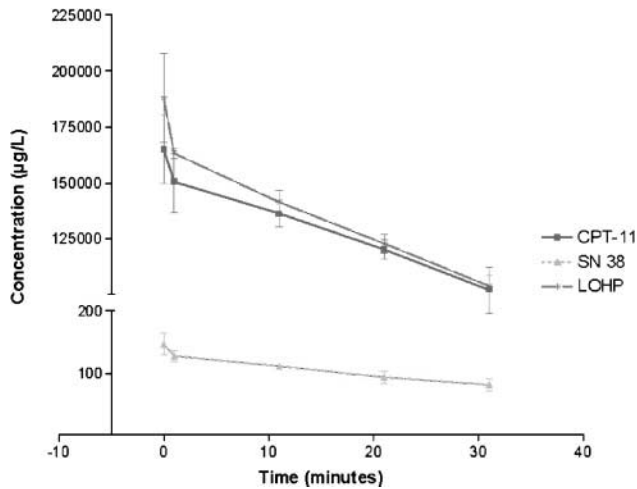


Figure 2. Decrease in CPT-11, SN 38 and oxaliplatin concentrations in heated peritoneal instillation (600 mg/m²).

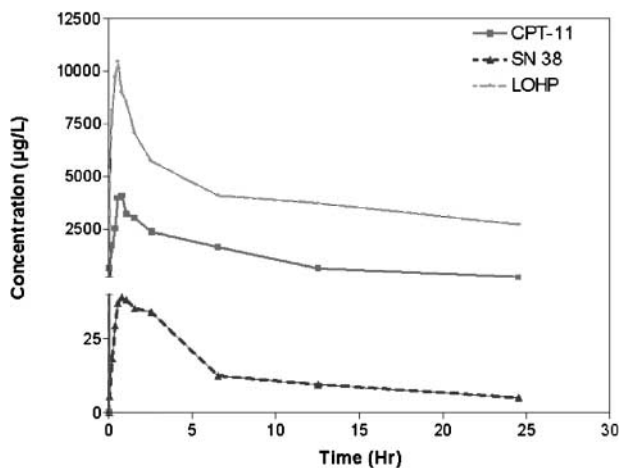


Figure 3. Irinotecan, SN 38 and LOHP pharmacokinetics in plasma after heated intraperitoneal chemotherapy (irinotecan dosage: 350 mg/m²).

the platinum plasmatic concentration peaked 30 min after starting IPCH. Subsequently, the platinum concentration dropped very rapidly, resulting in a limited systemic area under the curve (AUC) (Figure 3). So, the mean plasmatic AUC of ultrafiltered platinum ($14.8 \pm 3.8 \mu\text{g/ml/h}$) was close to that obtained with systemic intravenous oxaliplatin over 2 h

Table 2. Percentage of irinotecan that disappeared according to the dose of irinotecan (in $\mu\text{g/l} \times 1000$) in the peritoneal solution at the beginning and end of IPCH (mean of five patients per dose level)

i.p. irinotecan (mg/m ²)	At the beginning of IPCH ^a	At the end of IPCH ^b	% irinotecan that disappeared
300	81.6	45.1	44.7
350	133.2	74.4	44.3
400	97.4	53.6	44.9
450	151.7	81	46.7
500	155.6	79.8	48.7
600	164.8	91.8	44.5
700	209.8	108.8	48.3

^aBefore the 5–10 min necessary to reach the i.p. temperature of 43°C.

^bAfter 30 min of IPCH at 43°C.

i.p., intraperitoneal; IPCH, intraperitoneal chemohyperthermia.

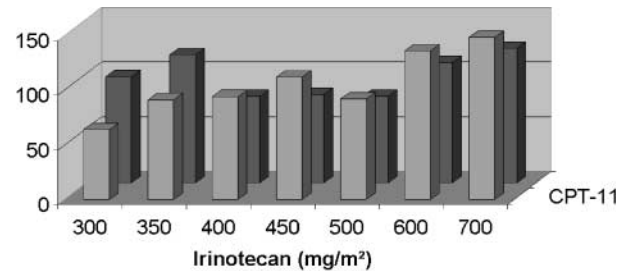


Figure 4. Peritoneal concentrations of irinotecan (mg/l) and SN-38 ($\mu\text{g/l}$) 10 min after the beginning of IPCH. CPT-11, light grey bars; SN-38, dark grey bars.

at 130 mg/m² ($11.9 \pm 4.60 \mu\text{g/ml/h}$). In solid tissues (tumor, peritoneum in contact with the drug and distant muscle), ultra-filterable platinum concentrations were higher in bathed than non-bathed tissues (ratio = 17.8). Platinum concentrations were similar in thin tumor tissue and peritoneum.

Pharmacokinetics of irinotecan and SN-38

Time course of irinotecan and SN-38 in the peritoneal perfusion. The concentration of irinotecan presented a rapid, constant and exponential decrease during the procedure (Figure 2). At the end of IPCH, 45–50% of the molecule was absorbed (Table 2). It is interesting to note that SN-38 was present in the peritoneal chemotherapy solution immediately after the beginning of the procedure and then stayed at a constant level (Figure 4). The effect of dose escalation resulted in increasing concentrations of irinotecan and SN-38 (Figure 4).

Time course of irinotecan and SN-38 in the blood. In the peripheral blood, we observed the peak plasma concentration 30 min after starting IPCH (Figure 3). Subsequently, the concentrations dropped very rapidly, resulting in a limited systemic AUC. The dose escalations resulted in increasing concentrations of irinotecan and SN-38 in the plasma (Figure 5). In addition, the mean plasmatic AUC of irinotecan ($16.8 \pm 3.8 \mu\text{g/ml/h}$) was slightly lower than that obtained with

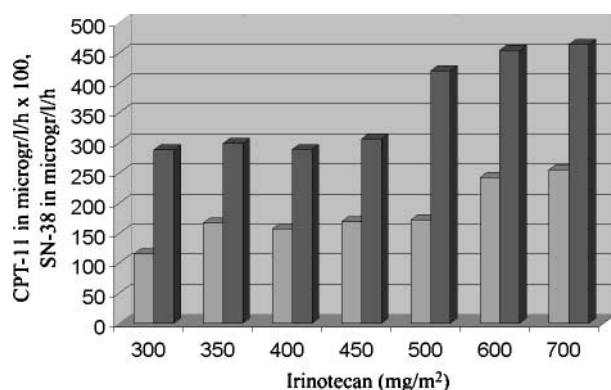


Figure 5. AUC of irinotecan (CPT-11) and SN-38 in plasma according to the doses of i.p. irinotecan (CPT-11 in $\mu\text{g/l/h} \times 100$, SN-38 in $\mu\text{g/l/h}$). CPT-11, light grey bars; SN-38, dark grey bars.

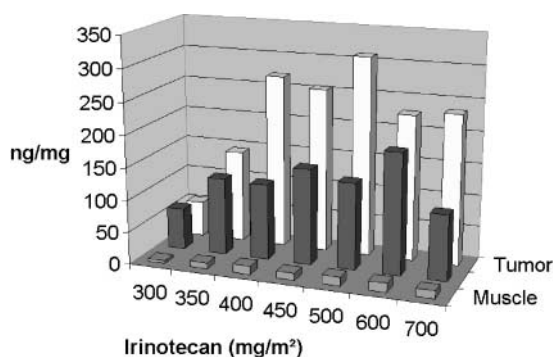


Figure 6. Intra-tissue irinotecan according to the increase in i.p. concentration of the molecule. Muscle, light grey bars; peritoneum, dark grey bars; tumour, white bars.

Table 3. Irinotecan concentration ratios between tumor (bathed with IPCH) and muscle (non bathed with IPCH)

	Dose of i.p. irinotecan (mg/m ²)						
	300	350	400	450	500	600	700
Ratio (tumor/muscle)	15.9	15.8	20.9	23.2	22.1	16.8	18.8

IPCH, intraperitoneal chemohyperthermia; i.p., intraperitoneal.

systemic intravenous irinotecan over 30 min at 350 mg/m² ($24.8 \pm 2.60 \mu\text{g/ml/h}$).

Tissue concentration of irinotecan. The concentration of irinotecan in solid tissues (tumor, peritoneum in contact with the drug and distant muscle) is reported in Figure 6. Concentrations were higher in bathed tissues than in non-bathed ones and surprisingly, among bathed tissues, higher in the tumor than in the peritoneum. The drug concentration in tumorous tissue progressively increased with doses from 300 to 400 mg/m², but seemed to stay constant for doses higher than 400. The different concentration ratios between the tumor (bathed with IPCH) and the muscle (non-bathed tissue) are reported in Table 3. They were 16–23 times higher in bathed

tissues than in non-bathed tissues, and not significantly different according to the dosages of intraperitoneal irinotecan.

Clinical results

Although not representing the primary goal of the study, we present them shortly. Among the 20 patients with colorectal PC, at a mean follow-up of 18.4 months (range: 12–24), two patients died of cancer recurrence, nine were alive with recurrence, and nine were alive and disease-free. Among the 11 patients with peritoneal pseudomyxoma (mean follow-up: 16.9 months, range: 12–24), one died postoperatively and the other 10 were free of disease.

Discussion

This trial is the first to report the intraperitoneal pharmacokinetics and tolerance of irinotecan plus oxaliplatin administered intraperitoneally, along with hyperthermia, in humans.

Intraperitoneal administration of chemotherapy drugs permits high local concentrations and good drug penetration in local superficial tissues, while decreasing systemic toxicity [9, 10]. The rationale for using IPCH immediately after a primary complete cytoreductive surgery is well established and has been described in previous studies [1–5, 10]. It concerns selected patient population sustaining a good general status and presenting completely resectable peritoneal disease.

Oxaliplatin and irinotecan are currently the most interesting drugs for colorectal carcinomas. Their association with intravenous 5-FU and leucovorin result in a synergic tri-therapy that may cure infra-millimetric deposits of tumor. This tri-therapy, when used intravenously in metastatic colorectal patients, resulted in 57–78% of objective responses [29–31]. Also, both oxaliplatin [32] and irinotecan [33] compound activities are potentiated by hyperthermia. Clearly, this aggressive treatment of PC, consisting in associating heavy cytoreductive surgery with regional hyperthermic chemotherapy, is the last opportunity to cure an advanced disease. It appears as a last resort treatment that one should not miss. In such conditions, it is justified to accept a high-risk treatment if proven to be efficient. We thought that such a tri-therapy was the most interesting treatment to evaluate, even if we knew that tolerance could be problematic.

The choice of a 30-min procedure at an effective temperature of 43°C, with rigorous quality control, was based on our previous experience with IPCH using other agents. After testing seven different procedures of IPCH in humans, we selected the open abdominal cavity technique with the skin retracted upwards. Our studies showed this method to optimize thermal homogeneity and a uniform fluid distribution throughout the peritoneal cavity. This is in contrast to the procedures performed in a closed cavity [27]. IPCH duration was then 60 min. In this study, we chose to increase drug concentrations and decrease IPCH duration to obtain a similar pharmacokinetic result, while maintaining plasma levels below those of historical intravenous controls, in order to decrease systemic toxicity. Moreover, we intended to decrease duration of surgery and therefore costs.

We proved in this trial that during IPCH, oxaliplatin and irinotecan were rapidly absorbed: half the dose administered during the 40 min of the procedure was absorbed. The same percentage of absorption was observed after 90 min when using mitomycin C [34, 35]. When considering hyperthermia, this short duration (30 min) of IPCH never induced central hyperthermia and did not require specific refreshing of the patient. This finding is underlined in a recent study reporting no increase in the temperature of bathed tissues deeper than 1 mm between 10 and 80 min of IPCH [7].

We used oxaliplatin at the recommended dosage (460 mg/m^2) issued from our previous trial devoted to the pharmacokinetics of this molecule when administered in the peritoneum at 43°C during 30 min [20]. The addition of increasing doses of irinotecan in the instillation did not modify the pharmacokinetics of oxaliplatin and the tissue concentration ratio between bathed and non-bathed tissues remained stable at 17.8.

Until now, very few studies have reported the use of intraperitoneal irinotecan in humans, and never in association with surgery, hyperthermia or oxaliplatin. Irinotecan is a pro-drug that exerts its anticancer activity after transformation into SN-38 by carboxylesterases. SN-38 is 100- to 1000-fold more cytotoxic than irinotecan. However, a recent study reported carboxylesterases to be minimally present in the peritoneum, and this would explain the similar response of carcinomatosis to intraperitoneal versus intravenous irinotecan [36]. Our findings were somehow different since we showed that SN-38 was detected in the peritoneal instillation in the first minute of IPCH and remained at a high constant level during the whole procedure (Figure 4). Similarly, it was rapidly detected in the plasma (Figure 2) and the intraperitoneal dose escalations resulted in increasing intravenous concentrations (Figure 5). Furthermore, we demonstrated that the intra-tumoral penetration of irinotecan was important and effective after tissue bathing (Figure 6), and that the tissue concentration ratio between bathed and non-bathed tissues ranged from 17 to 23. This result is similar to the ratio of 17.8 obtained with oxaliplatin. Finally, during this 40-min procedure, 50% of both irinotecan and oxaliplatin administered intraperitoneally were absorbed by the patient. While observing a dose-effect in peritoneal and in plasmatic concentrations of irinotecan during the initial dose escalations (Figures 3 and 5), the tissue concentration did not increase after 400 mg/m^2 (Figure 6).

This trial, albeit successful in terms of pharmacokinetics, underlines unsolved questions concerning tolerance. Mortality (2.5%) and non-hematological morbidity (26%) rates were low and expected. On the other hand, the grade 3–4 hematological toxicity rate was 58%, with 41% (16/39) grade 4 neutropenias ($<500/\text{mm}^3$) and 26% (10/39) grade 3 thrombopenias ($<50\,000/\text{mm}^3$). These situations are always risky, even if we did not observe any lethal consequence in this trial. This toxicity was also present with lower doses of intraperitoneal irinotecan but to a lesser extent. It is worth mentioning that high hematological toxicity rates were also reported during systemic use of this tri-therapy [29–31, 37].

Surprisingly, the hematological toxicity was neither correlated to the dose of irinotecan nor the duration of preoperative systemic chemotherapy. It was significantly correlated only with the extent of PC ($P=0.017$) and duration of surgery ($P=0.046$) (which were two tied factors, $P=0.01$): this should lead to reappraisal of the concept of capillary basement membrane as ‘peritoneal-plasma barrier’ [38], along with the assumption that peritoneal surface disruption has no real impact on drug absorption.

In conclusion, this study demonstrated that IPCH with oxaliplatin and irinotecan is feasible after complete cytoreductive surgery. The pharmacokinetic study revealed a dose-related systemic absorption and efficient intratumoral penetration of the two molecules. The recommended doses are set at 460 mg/m^2 of oxaliplatin and 400 mg/m^2 of irinotecan in a 2 l/m^2 instillation over 30 min at 43°C . A high rate of hematological complications should be expected. Other doses of these two molecules are currently being studied with the aim of decreasing hematological toxicity.

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