Efficacy of intraperitoneal chemohyperthermia with oxaliplatin in colorectal peritoneal carcinomatosis. Preliminary results in 24 patients

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Background: The complete resection of macroscopic colorectal peritoneal carcinomatosis (PC), followed by intraoperative intraperitoneal chemohyperthermia (IPCH) to treat residual microscopic disease, leads to cure in some patients. We report preliminary results on survival in a phase II study using oxaliplatin (LOHP).

Patients and methods: Twenty-four patients with macroscopic colorectal PC underwent complete resection of the PC followed by IPCH with LOHP performed in an open abdominal cavity. The dose of LOHP was 460 mg/m² in 2 l/m², during 30 min at 43°C, at a flow rate of 2 l/min. During the hour preceding IPCH, they received an intravenous administration of 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²).

Results: Mean peritoneal tumoral extension (Sugarbaker’s Index) was 16.9 ± 9.5, median operative duration was 490 min and median blood loss was 965 ml. There were two postoperative deaths (8%) by intracerebral hemorrhage, and morbidity rate was 41.6%. Minimal follow-up was 18 months and median follow-up was 27.4 months (range 18.3–49.6). At 1, 2 and 3 years, overall survival rates were 83%, 74% and 65%, and disease-free survival rates were 70%, 50% and 50%, respectively. Only 32% of the 22 postoperative living patients presented a peritoneal recurrence. A peritoneal index >24 influenced survival, with a 17% recurrence rate at 2 years versus 63% when it was <24 (P = 0.005).

Conclusion: This new modality of treatment, when feasible, gives encouraging preliminary results, with a promising 3-year survival rate of 65%.

Key words: colorectal, intraperitoneal chemohyperthermia, oxaliplatin, peritoneal carcinomatosis, surgery

Introduction

Peritoneal carcinomatosis (PC) is one of the most common causes of incurability of intra-abdominal cancers. Surgery or chemotherapy alone is not able to cure these patients. However, a new therapeutic concept [1] has already led to a definitive cure of some cases of PC [2–4]. This concept is to treat macroscopic PC with complete cytoreductive surgery and residual microscopic PC with intraperitoneal chemohyperthermia (IPCH). Complete cytoreductive surgery is necessary because experimental studies show that drug penetration is limited to a few cell layers under the surface of the tumor [5]. Intraperitoneal (i.p.) chemotherapy must be immediate, avoiding trapping residual tumor cells in the post-operative fibrin adhesions [6, 7]. IPCH leads to high local concentration of antineoplastic agents [8, 9], and their cytotoxicity is improved by hyperthermia [8, 9], that of oxaliplatin (LOHP) being increased by 180% [10].

LOHP, a third-generation platinum complex, is an interesting agent for IPCH in colorectal PC [11–13]. It belongs to the family of platins, which are frequently used in IPCH [8, 9, 14–16], and induces no renal or hepatic toxicity. In a previous trial, we performed a pharmacokinetic study of heated i.p. LOHP in humans. We established that 460 mg/m² of LOHP in 2 l/m² of iso-osmotic 5% dextrose, at 42–44°C during 30 min, given intraperitoneally after an intravenous (i.v.) infusion of 5-fluorouracil (400 mg/m²) with folinic acid (20 mg/m²), was well tolerated [17]. It was also pharmacologically interesting, with an intratumoral penetration 17.8-fold higher than in non-bathed tissue [17]. 5-Fluorouracil was given to potentiate the effect of LOHP [11–13], but could not be mixed intraperitoneally with it because of a pH incompatibility.

In a second trial in humans, we showed that using various i.p. hypotonic solutions had no pharmacokinetic advantage and resulted in frequent postoperative peritoneal hemorrhage [18].

In this study, we report the preliminary results of a phase II clinical study of complete cytoreductive surgery associated with IPCH with LOHP for colorectal PC. The results presented here concern only patients with a minimal follow-up of 18 months.

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Patients and methods

Patient eligibility
From June 1998 to February 2001, 30 consecutive patients with preoperatively identified colorectal PC were eligible for this prospective phase II trial. The protocol was reviewed and approved both by 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. Criteria of eligibility were a PC of colorectal origin, a good general status and age <65 years, no extra-abdominal extension, no evidence of bowel obstruction, no important ascitis and no bulky clinical or radiological PC. The presence of one or two liver metastases, easily resectable, was not a contraindication [19]. All patients had already received i.v. chemotherapy, including LOHP or irinotecan-based regimens, for at least 3 months. A rapid progression of the PC under i.v. chemotherapy was a contraindication. Preoperative work-up included a clinical rectal examination, a CT-scan of the thorax and abdomen, a complete colonoscopy and carcinoembryonic antigen (CEA) measurement. No Pet-scan imaging was carried out. The primary tumor had always been previously resected (mean delay between resection and IPCH was 11.2 ± 5.2 months), and the mean number of laparotomies per patient before the study (excluding the laparotomy treating the primary tumor) was 1.6 (median 1, range 0–5).

At laparotomy, we confirmed the diagnosis of PC by frozen section and scored the extent of PC according to Sugarbaker’s peritoneal index [14]. This index takes into account the number of invaded areas among a total of 13, and the maximal size of tumor nodules among three possible groups (<5 mm, 5 mm to 5 cm, >5 cm). Macroscopically detectable disease had to be completely resected before including the patient in the trial. However, remaining tumor seeding <2 mm diameter could be accepted when located on the small bowel or stomach. If, after an extensive exploration, we considered PC to be incompletely resectable, we did not include the patient in the study and no IPCH was carried out. This occurred in six of the 30 patients (20%) during this period.

Surgical procedures
Twenty-four patients were thus included in the study, eight men and 16 women, with a mean age of 50 ± 9.3 years. Seven of them had associated extra-peritoneal lesions: metastases in the liver (four patients), ovary (two patients) and spleen (one patient), which were resected during the same procedure. Resection of PC obeyed principles described elsewhere [20]. Intestinal anastomoses were delayed until after IPCH was carried out in order to treat the bowel margins. There were no temporary stomas.

Intraperitoneal chemohyperthermia
We performed 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 [16]. IPCH was carried out with the abdomen open, skin pulled upwards (after demonstrating in our institution that this technique was the only one to allow temperature homogeneity and complete spatial diffusion of the peritoneal instillation in the whole peritoneal cavity) [16]. Flow rate was 1l/min for each pump. Four thermal probes inside the peritoneal cavity gave continuous temperature feedback. We monitored the whole process and saved the data in a computer. The intra-abdominal temperature was maintained everywhere between 42°C and 44°C during IPCH. Perfusion duration was 30 min from the time when optimal temperature (42–44°C) was reached. Usually, <5 min were necessary to reach a high homogeneous temperature, leading to total peritoneal infusion duration of ∼35 min. Afterwards, we completely evacuated the infusion. We delivered the total LOHP dose as a bolus mixed with 5% dextrose at the beginning of the procedure. The total amount of peritoneal liquid used was based, as for LOHP, on the body surface area: 2 l/m². Dosage of LOHP was 460 mg/m², as recommended in our previous study in humans [17]. Determination of instillation volume and of LOHP dosage, both based on measurement of body surface area (in m²), resulted in a similar intraperitoneal concentration of drug in each patient. One hour before IPCH, we delivered systemic i.v. leucovorin (LV) 20 mg/m² and 5-fluorouracil (5-FU) 400 mg/m² because 5-FU potentiates the action of LOHP [12] and because 5-FU cannot be mixed with LOHP in the peritoneal cavity due to pH incompatibility. Following this systemic infusion, tumor and healthy tissue were soaked with 5-FU before the beginning of IPCH.

Adjuvant i.v. chemotherapy
Following IPCH, systemic chemotherapy, similar to the preoperative one, was delivered for 3–6 months, depending on their tolerance, to patients who preoperatively presented an objective response (>50%).

Postoperative morbidity
Complications were graded according to the classification of Feldman et al. [21]. Grade 1 complications, defined as minor (i.e. complications which resolve if left untreated or which require simple bedside procedure without drugs except analgesics, antipyretics, anti-diarrheals or oral antibiotics), were not included.

Statistics
Patients were recorded prospectively in a specific database. Follow-up was every 3 months, with rectal examination and CEA measurements. A CT-scan of the abdomen and thorax and abdominal ultrasonography were performed alternatively every 6 months. The exact status of each patient was clear at the date of analysis of the series (September 2002). Minimal follow-up was 18 months for each patient. No patient was excluded from survival analyses (including postoperative deaths). The chi square test or Fisher’s exact test, when appropriate, were used for univariate comparisons. Survival curves were calculated with the Kaplan–Meier method and compared with the log-rank test. Differences were considered significant at P = 0.05.

Results

Intraoperative data
Intraoperative data are reported in Table 1 (number of invaded peritoneal areas among the 13 areas described by Sugarbaker, peritoneal index, resected organs, digestive anastomoses, duration of surgery and blood loss). Before resection, maximal size of tumor nodules was >5 cm diameter (or diffuse in one whole area) in 14 patients, between 5 cm and 5 mm in nine, and <5 mm in one. After resection, the size of residual tumor seeding was 0 mm in 15 patients, 1 mm in eight and 2 mm in one. There were 10 low rectal anastomoses, under the level of the cul-de-sac of Douglas, and three total colectomies. Seven patients had associated extra-peritoneal metastases, which were resected at the same time (liver, four; ovary, two; spleen, one). Only complete invasion or deep localization (not superficial) in the ovary were considered as distant metastases and not peritoneal implant. Liver resections never implicated more than one-third of liver mass.

Perioperative mortality and morbidity
Perioperative mortality and morbidity was assessed until patients left the hospital. Two patients died postoperatively (8.3%) of cerebral hemorrhage. One was due to a severe thrombocytopenia and the other to rupture of a cerebral aneurysm. Grade 2 or 3 morbidities occurred in nine patients (total morbidity 41.6%) and are
detailed in Table 2. One patient needed a relaparotomy for pancreatic fistula and one needed two relaparotomies for digestive fistula.

**Survival results, recurrences and prognostic study**

Mean follow-up was 27.4 months (range 18.3–49.6). One patient, without any evidence of recurrence, committed suicide 8 months after surgery. Overall survival rates at 1, 2 and 3 years were, respectively, 83%, 74% and 65%, and disease-free survival rates were, respectively, 61%, 50% and 50% (Figure 1). The incidence of peritoneal recurrence at 1, 2 and 3 years was 11%, 32% and 32% for the 22 surviving patients. Six of the seven peritoneal recurrences were isolated and one was associated with liver metastases (this patient had two liver metastases at IPCH). Extraperitoneal recurrences were in the liver (n = 3; all these patients had liver

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### Table 1. Intraoperative data of the 24 patients treated with complete cytoreductive surgery followed by IPCH with LOHP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of invaded areas(^a)</td>
<td>9.08</td>
<td>4.08</td>
<td>10</td>
<td>2–13</td>
</tr>
<tr>
<td>Peritoneal index(^b)</td>
<td>16.9</td>
<td>9.5</td>
<td>13.9</td>
<td>4–35</td>
</tr>
<tr>
<td>No. of resected organs</td>
<td>4.54</td>
<td>2.1</td>
<td>5</td>
<td>1–8</td>
</tr>
<tr>
<td>No. of circular anastomosis</td>
<td>1.5</td>
<td>0.97</td>
<td>1.5</td>
<td>0–3</td>
</tr>
<tr>
<td>No. of lateral sutures</td>
<td>1.75</td>
<td>1.15</td>
<td>2</td>
<td>0–5</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>485</td>
<td>172</td>
<td>490</td>
<td>220–868</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>1276</td>
<td>917</td>
<td>965</td>
<td>400–4100</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>25.5</td>
<td>8.6</td>
<td>23</td>
<td>10–45</td>
</tr>
</tbody>
</table>

\(^a\)Among the 13 intra-abdominal areas.

\(^b\)This index can range from 1 to 39. The 13 areas of the abdominal cavity are scored as follows: 0 when there was no tumor deposit, 1 when tumor deposit was between 0 and 5 mm, 2 when tumor deposit was between 5 mm and 5 cm, and 3 when tumor deposit was >5 cm or diffuse [14].

IPCH, intraperitoneal chemohyperthermia; LOHP, oxaliplatin; SD, standard deviation.

### Table 2. Postoperative morbidity\(^4\) and mortality after IPCH with LOHP (24 patients)

<table>
<thead>
<tr>
<th>Types (n)(^b)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal complications(^c)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Digestive fistula (1)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic fistula (1)</td>
<td></td>
</tr>
<tr>
<td>Urinary fistula (1)</td>
<td></td>
</tr>
<tr>
<td>Abscess (1)</td>
<td></td>
</tr>
<tr>
<td>Retropertitoneal hematoma (1)</td>
<td></td>
</tr>
<tr>
<td>Transient vesical incontinence (1)</td>
<td></td>
</tr>
<tr>
<td>Extra-abdominal complications</td>
<td>9 (37.5%)</td>
</tr>
<tr>
<td>Cerebral hemorrhage (2)</td>
<td></td>
</tr>
<tr>
<td>Aplasia (grade 2–3) (2)</td>
<td></td>
</tr>
<tr>
<td>Lung infection (2)</td>
<td></td>
</tr>
<tr>
<td>Occlusive microangiopathy (1)</td>
<td></td>
</tr>
<tr>
<td>Catheter infection (1)</td>
<td></td>
</tr>
<tr>
<td>Transient renal failure (1)</td>
<td></td>
</tr>
<tr>
<td>Deficit of the external sciatic popliteal nerve (1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 (41.6%)</td>
</tr>
<tr>
<td>Intra and extra-abdominal complications (4)</td>
<td></td>
</tr>
</tbody>
</table>

\(^4\)Only grade 2 and 3 complications according to Feldman et al. [21] were collected. Grade 1 complications (i.e. minor complications which resolve if left untreated or which require simple bedside procedure without drugs except analgesics, antipyretics, antiarrheals or oral antibiotics) were not counted.

\(^b\)Different types of complications could be associated in the same patient.

\(^c\)One patient needed one relaparotomy (pancreatic fistula) and one needed two relaparotomies (digestive fistula).

IPCH, intraperitoneal chemohyperthermia; LOHP, oxaliplatin.
metastases at IPCH), in the lung (n = 3; one had liver metastases at IPCH), and in hilar lymph nodes (n = 1). The peritoneal extension of the disease (when the peritoneal index was >24) had a significant prognostic impact on recurrence (P = 0.005), but the presence of associated visceral metastases did not (P = 0.42; Figure 2).

**Discussion**

With an overall survival rate of 74% and an incidence of peritoneal recurrence of 32% at 2 years, the results of this series are far better than the classical ones. PC from colorectal cancer is generally considered as an incurable disease, and standard treatment is systemic chemotherapy. Median survival is ~6 months with a 5-FU-based chemotherapy [22], and nearer 1 year with new regimens of chemotherapy including irinotecan or oxaliplatin. However, for selected patients, the association of an almost complete resection with IPCH leads to a cure [2, 4]. Sugarbaker et al. reported a study on 29 patients with complete cytoreduction and IPCH using i.p. mitomycin C with a 5-year survival rate of 37% [2]. We reported a 5-year survival rate of 28% in 54 similar patients treated with i.p. mitomycin C ± cisplatin with early post-operative i.p. chemotherapy (without hyperthermia), or with non-optimal IPCH (phase I trial to define the best technique to perform IPCH) [4, 16].

More interesting are the preliminary results of the randomized trial of Zoetmulder et al. comparing standard treatment (systemic chemotherapy) to cytoreductive surgery with IPCH using mitomycin C in 104 colorectal patients. The 2-year survival rate in each group was, respectively, 16% and 43% (P = 0.01), while many patients in the treated group could not benefit from a complete resection of their PC [23]. This phase III study definitively demonstrated the superiority of this new approach. It also underlined the fact that a complete cytoreductive surgery is possible in only some patients with colorectal PC. In our study, the impossibility of resecting all tumor nodules >2 mm was a criteria of exclusion, because IPCH acts only in superficial tissues [5]. Besides, only one of the 24 patients had residual tumor nodules measuring between 1 and 2 mm. Currently, IPCH, which is an aggressive treatment, is indicated to treat only a millimetric residual disease after maximal cytoreductive surgery.

Nevertheless, mitomycin C (which is used extensively worldwide for IPCH) is not considered a very active drug for colorectal cancers, unlike LOHP [24, 25]. It was therefore logical to use LOHP for IPCH. We thus conducted a first trial in humans to study the pharmacokinetics of heated i.p. LOHP in order to define the suitable dosage and tolerance [17]. The dose used in the present study and the addition of i.v. 5-FU and LV represent the direct application of our results. Half the dose of i.p. LOHP was absorbed in 30 min, and tumoral tissue concentration of LOHP was 18-fold higher in bathed tissues than in non-bathed ones [17]. We did not use any hypotonic solution in our study, because we demonstrated in another human trial that it had no pharmacokinetic advantage and frequently resulted in local postoperative hemorrhage [18].

When looking at prognostic factors, a peritoneal index >24 could be a new and promising one: in our series, only one of the six patients with such a score did not recur. This leads to the hypothesis that, maybe in the future, the presence of liver metastases and/or a peritoneal index >24 could represent a relative contraindication to this approach. However, more extensive data are necessary to confirm these findings.

The efficacy of peritoneal mixing can still be improved because polychemotherapies are more potent than monotherapies. This is the reason why we are currently conducting a phase I trial combining LOHP with irinotecan during IPCH in humans. However, at this date, our biggest challenge is to select the right patients for this approach: it is necessary to detect infraclinic extraperitoneal disease and also to appreciate the real extent of the PC before operating.

In conclusion, IPCH with LOHP, after complete resection of PC, gave encouraging therapeutic results and is able to cure definitively a high proportion of selected patients.

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References


