Peritoneal carcinomatosis of colorectal origin

Long-term results of intraperitoneal chemohyperthermia with oxaliplatin following complete cytoreductive surgery

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SUMMARY

Purpose — Complete resection of macroscopic colorectal peritoneal carcinomatosis (PC) is followed by intraoperative intraperitoneal chemohyperthermia (IPCH) to treat residual microscopic disease and achieve cure in some patients. We report long-term results concerning survival of a phase II study using oxaliplatin (LOHP).

Patients and methods — From June 1998 to December 2003, thirty patients with macroscopic colorectal PC underwent complete resection of PC followed by IPCH with LOHP performed in an open abdominal cavity. The dose of LOHP was 460 mg/m² in 2 L/m² of iso-osmotic 5% dextrose, over 30 min at an intraperitoneally homogenous temperature of 43°C and at a flow rate of 2 L/min in the continuous closed circuit. During the hour preceding IPCH, patients received 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) intravenously. All patients received neoadjuvant and adjuvant systemic chemotherapy.

Results — Mean peritoneal tumor extension (Sugarbaker’s Score) was 14.3 ± 3.8, median operative duration, 450 min, and median blood loss, 940 mL. Eleven (37%) patients had associated extra-peritoneal lesions which were resected during the same procedure. There were no postoperative deaths and grade 2-3 morbidity (requiring specific treatment) was 40%. Median follow-up was 55 months (range: 31-84). Twenty-two patients (73%) relapsed after a median interval of 14 months, but 7 of them (32%) were amenable to curative repeat surgery. At 3 and 5 years, overall survival rates (95% confidence interval) were 53% (9-72), and 48.5% (31-66) respectively. At 3 and 5 years, disease-free survival rates were 41.5% (27-59), and 34% (19-52) respectively. Median survival was 60.1 months.

Conclusion — When feasible, this treatment modality yields a 5-year survival rate of 48.5%, with median survival attaining 60.1 months.

RéSUMÉ

Carcinomatose péritonéale d’origine colorectale

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But de l’étude — La résection chirurgicale complète d’une carcinose péritonéale (CP) macroscopique, suivie d’une chimio-hyperthermie intrapéritonéale peropératoire (CHIP) pour traiter la maladie résiduelle microscopique permet de guérir un certain nombre de malades. Le but de cette étude de phase II est de rapporter la survie à 5 ans d’une série de malades pour lesquels l’oxaliplatine (LOHP) a été utilisée pour la CHIP.

Malades et méthodes — De juin 1998 à décembre 2003, trente malades consécutifs qui étaient porteurs d’une CP macroscopique d’origine colorectale ont eu l’extension complète de cette CP suivie d’une CHIP réalisée à ventre ouvert, peau en traction vers le haut, avec du LOHP. Les doses de LOHP étaient de 460 mg/m² dans du glucose iso-osmotique à 5 %, pendant 30 min à une température intrapéritonéale homogène de 43°C, avec un débit de 2 L/min en circuit fermé. Durant l’heure qui précédaient la CHIP, les malades recevaient une perfusion iv de 5-fluorouracil (400 mg/m²) et d’acide folinique (20 mg/m²). Tous les malades ont reçu également une chimiothérapie systémique néoadjuvante et adjuvante.

Résultats — Le score moyen d’extension de la CP (selon l’index de Sugarbaker) était de 14.3 ± 3.8, la durée médiane de l’intervention de 450 min, et la perte sanguine médiane de 940 mL. Onze (37 %) des malades présentaient également des lésions tumorales extrapéritonéales qui ont été réséquées durant la même procédure. Il n’y eut aucun décès postopératoire et la morbidité de grade 2-3 compliquant le traitement spécifique a été de 40 %. Le suivi médian était de 55 mois (extrêmes: 31-84). Vingt-deux malades (73 %) ont récidivé après un délai moyen de 14 mois, mais 7 d’entre eux (32 %) ont pu être réopérés dans un but curateur. A 3 et 5 ans, les survies globales (avec un intervalle de confiance de 95 %) étaient respectivement 53 % (9-72) et 48,5 % (19-52). A 3 et 5 ans les survies sans récidives étaient respectivement de 41,5 % (27-59) et 34 % (19-52). La médiane de survie était de 60,1 mois.

Conclusion — Quand un tel traitement est réalisable, il permet d’obtenir une survie à 5 ans de 48,5 % et une médiane de survie atteignant 60,1 mois.
xicity of oxaliplatin (LOHP) is increased by 180% [10]. Finally, we need to be certain that a single administration of short-duration high-dose chemotherapy is able to kill all remaining tumor cells. Mitomycin C and cisplatin are usually used for IPCH but LOHP is considerably more efficient against colorectal cancers [8, 11]. LOHP, a third generation platinum complex, is a very 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 is not renotoxic or hepatotoxic. We previously performed a pharmacokinetic trial of heated i.p. LOHP in humans [17] and established that 460 mg/m² of LOHP in 2 L/m² of iso-osmotic 5% dextrose, at 42-44°C over 30 minutes, given intraoperatively after an intravenous (i.v.) infusion of 5-fluorouracil (5-FU) (400 mg/m²) with leucovorin (20 mg/m²), was well tolerated. It was also interesting from a pharmacological point of view, with intratumor penetration 17.8-fold higher than in unbathed tissue.

In 2004, we published the preliminary results of a trial in 24 patients treated with this regimen which yielded a promising 2-year survival rate of 74% (and 50% of disease-free patients) [18]. However, this first study included patients with grade 3 (considered malignant) peritoneal pseudomyxoma originating from the appendix and the follow-up was short. With experience, we and other authors consider that PC originating from the colon-rectum and pseudomyxoma originating from the appendix give rise to different therapeutic problems and results. The high mortality and morbidity rates observed in our preliminary study after mandatory extensive cytoreductive surgery to resect the pseudomyxoma is ample proof of this difference: the two postoperative deaths and the most severe complications occurred in this subgroup of patients [18].

In this study, we report the long-term results of a phase II study of LOHP (460 mg/m²) during IPCH following complete cytoreductive surgery in patients with colorectal PC. Peritoneal pseudomyxomas, whatever the grade, were excluded.

Patients and methods

Patient eligibility

Between June 1998 and December 2002, thirty consecutive patients (9 men and 21 women, mean age 49.8 ± 9.8 years) with macroscopic colorectal PC underwent complete resection of PC followed by IPCH. The origin of PC was colic in 24 patients and rectal in 6. The protocol was reviewed and approved both by our Institutional Review Board and by an independent Ethics Committee. All patients gave their written informed consent for participation in the study. Eligibility criteria were as follows: PC of colorectal origin (peritoneal pseudomyxomas were excluded, whatever the grade), a good general status and age below 65 years, no extra-abdominal extension, no occlusive disorders, no abundant ascites, and no bulky clinical or radiological PC. All patients had previously received intravenous chemotherapy containing LOHP or irinotecan for at least 3 months. Rapid progression of PC under i.v. chemotherapy was a contraindication. Patients who achieved an objective response received the same regimen postoperatively over 4 to 6 months. The preoperative work-up included a clinical rectal examination to evaluate Douglas pouch involvement, a CT scan of the thorax and abdomen, a complete colonoscopy, and CEA measurement. No PET scan imaging was done. The primary tumor was always 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).

Surgical procedures

At laparotomy, we confirmed the diagnosis of PC by frozen section analysis and scored the extent of PC according to Sugarbaker’s peritoneal index [14]. Macroscopically detectable disease had to be completely resected before including the patient in the trial. However, any remaining tumor seeding smaller than 2 mm in diameter was considered acceptable when located on the small bowel or stomach. Resection of PC obeyed principles described elsewhere [19]. Intestinal anastomoses were delayed until after IPCH in order to treat bowel margins. If PC was deemed incompletely resectable after extensive exploration, the patient was not included in the study and no IPCH was performed. Such was the case in 8 patients during this period (8/38=21%). Eleven (37%) patients had associated extra-peritoneal lesions in the liver (N = 5), the ovari (N = 4) and spleen (N = 2); these additional lesions were resected during the same procedure.

Intraperitoneal chemohyperthermia and intravenous chemotherapy

LOHP was administered at a dose of 460 mg/m² in 2 L/m² of iso-osmotic 5% dextrose. This solution was administered intraperitoneally in an open abdominal cavity (Coliseum technique). We used a continuous closed circuit with four 36-French drains (two inlets and two outlets) connected to two pumps, one heating unit and two heat exchangers to eliminate a Y connector that could have reduced flow rates and heat homogeneity [16]. Intraperitoneal temperature was homogeneous at 43°C (range: 42-44°C) for 30 minutes (strictly 30 min as soon as the minimum temperature of 42°C had been reached throughout the abdominal cavity, plus 5 to 8 min before to heat the infusate from 38°C to 42°C). Patients received an intravenous perfusion of 5-fluorouracil (5-FU) (400 mg/m²) with leucovorin (20 mg/m²) before starting IPCH. 5-FU potentiates the activity of LOHP but as it cannot be mixed with the latter inside the peritoneal cavity (pH incompatibility) it was administered intravenously. Thus, tumor and healthy tissue were soaked with this systemic infusion of 5-FU before the beginning of the IPCH.

Adjuvant i.v. chemotherapy

After the procedure, systemic chemotherapy similar to that given preoperatively, was administered over 3 to 6 months, depending on tolerance, to patients who had achieved an objective response before surgery (> 50%).

Postoperative morbidity

Complications were graded according to the classification established by Feldman et al. [20]. Grade 1 complications, defined as minor (i.e. complication that resolved if left untreated or required a simple bedside procedure without drugs with the exception of analgesics, anti-pyretics, anti-diarrheals or oral antibiotics), were not included.

Follow-up and Statistics

Patients were recorded prospectively in a specific database. Follow-up was every 3 months, with a rectal examination and CEA measurement. A CT scan of the abdomen and thorax and abdominal ultrasound were performed alternately every 6 months. The exact status of each patient was known on the date of the analysis of the series (December 2005). Minimal follow-up was 36 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 described by Sugarbaker, the scored peritoneal index, resected organs, digestive anastomoses, duration of surgery, and blood loss). After resection, the maximal size of tumor nodules exceeded 5 cm in diameter (or nodules were diffuse in an entire area) in 14 patients, between 5 mm and 5 cm in 13, and smaller than 5 mm in 3. After resection, the size of residual tumor seeding was 0 mm in 19 patients, and < 2 mm in 11. A low rectal anastomosis, below the level of the Pouch of Douglas, was performed in 10 patients, and 3 patients underwent a total colectomy. Eleven (37%) patients had associated extra-perito-
neal lesions, located in the liver (N = 5), the ovary (N = 4) and spleen (N = 2); which were resected during the same procedure. Only complete invasion or deep-seated lesions (not superficial) in the ovary were considered as distant metastases and not as peritoneal implants. Liver resections never involved more than one-third of the liver mass.

**Perioperative mortality-morbidity**

They were assessed until patients were discharged from hospital. There were no postoperative deaths (0%), and grade 2-3 morbidity (requiring specific treatment) was 40%. It occurred in 12 patients and is detailed with the corresponding treatment in table II.

**Survival results, recurrences and prognostic study**

Mean follow-up was 55 months (range: 24-80). One patient, with no sign of recurrence, committed suicide 8 months after surgery. Twenty-two (73%) patients relapsed after a median interval of 14 months (range 2-46), 11 of them (37%) developed a peritoneal recurrence (3 times associated with an extra-peritoneal recurrence) that was diagnosed clinically or radiologically. Seven of these 22 patients (32%) were amenable to curative repeat surgery (liver: 2, peritoneum: 2, lung: 2, and spleen: 1). Patients with unresectable recurrences were treated with i.v. chemotherapy. Contrary to all expectations, one of them achieved a complete response of multiple small lung metastases that had been present for two years. At 2, 3 and 5 years, overall survival rates

Table I. – Intraoperative data of the 30 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>Nb of invaded areas*</td>
<td>8.3</td>
<td>3.8</td>
<td>9</td>
<td>2-13</td>
</tr>
<tr>
<td>Peritoneal index**</td>
<td>14.3</td>
<td>8.2</td>
<td>12</td>
<td>4-36</td>
</tr>
<tr>
<td>Nb of resected organs</td>
<td>4.2</td>
<td>1.9</td>
<td>4</td>
<td>1-9</td>
</tr>
<tr>
<td>Nb of circular anastomoses</td>
<td>1.4</td>
<td>1</td>
<td>1</td>
<td>0-4</td>
</tr>
<tr>
<td>Nb of lateral sutures</td>
<td>1.8</td>
<td>1.8</td>
<td>1.5</td>
<td>0-9</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>457</td>
<td>140</td>
<td>450</td>
<td>220-840</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>1112</td>
<td>717</td>
<td>940</td>
<td>300-2800</td>
</tr>
<tr>
<td>Duration of hospitalization (d)</td>
<td>23.6</td>
<td>8.8</td>
<td>21</td>
<td>12-56</td>
</tr>
</tbody>
</table>

* Among the 13 intra-abdominal areas.

** This index can range from 1 to 39. The 13 areas of the abdominal cavity are scored as follows: 0 when there is no tumor deposit, 1 when the tumor deposit is between 0 and 5 mm, 2 when the tumor deposit is between 5 mm and 5 cm, and 3 when the tumor deposit is greater than 5 cm or diffuse [14].

IPCH: intraperitoneal chemohyperthermia; LOHP: oxaliplatin.

Table II. – Postoperative morbidity1 after IPCH with LOHP (n = 30 patients).

<table>
<thead>
<tr>
<th>Nb of pts (%)</th>
<th>Types2</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Digestive fistula: 4</td>
<td>Repeat surgery: 3</td>
</tr>
<tr>
<td>Complications</td>
<td>Pancreatic fistula: 1</td>
<td>Percutaneous drain</td>
</tr>
<tr>
<td></td>
<td>Urinary fistula: 1</td>
<td>Ureteral drain</td>
</tr>
<tr>
<td></td>
<td>Profound abscess: 1</td>
<td>Percutaneous drain</td>
</tr>
<tr>
<td>Extra-abdominal complications</td>
<td>Lung infection: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aplasia (grade 2-3): 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter infection: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transient renal failure: 1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>External sciatic popliteal nerve deficit: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (40%)</td>
<td>3 of them had intra- and extra-abdominal complications</td>
</tr>
</tbody>
</table>

1 Only grade 2 and grade 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 procedures without drugs excepted analgesics, antipyretics, antiarrheals or oral antibiotics) were not counted.

2 Different types of complications could be associated in the same patient.

IPCH: intraperitoneal chemohyperthermia; LOHP: oxaliplatin.
(95% confidence interval) were 73% (59-88), 53% (9-72), and 48.5% (31-66) respectively. At 2, 3 and 5 years, disease-free survival rates were 48% (32-66), 41.5% (27-59), and 34% (19-52) respectively (figure 1). Median survival was 60.1 months.

In this small series, neither the site of the primary cancer (colic or rectal), nor the extent of the PC (peritoneal index), nor the presence of (resected) metastases inside the liver, spleen or ovary, had a significant prognostic impact on overall or disease-free survival.

Discussion

With a 5-year overall survival rate of 48.5%, a 5-year disease-free survival rate of 34%, median survival attaining 60.1 months, this short series provides four new and important findings.

First, some patients with colorectal PC can be cured with complete cytoreductive surgery combined with IPCH, and the impact of this combined treatment on survival is far greater than previously thought. Recently, Verwaal et al. reported a 5-year survival rate of 43% (median survival: 42.9 months) in 59 patients who underwent macroscopically complete cytoreduction plus IPCH with mitomycin C at 40°C to 41°C for 90 min [21]. In contrast, the 5-year survival rate was 0% when gross macroscopic tumor was left behind, despite IPCH [21]. Piso et al. also reported a 75% 4-year survival rate [22]. These concordant results reported by different teams now provide substantial evidence that this aggressive approach combining 2 treatment modalities is able to cure PC of colorectal origin.

Second, only selected patients are likely to benefit from this treatment. Our patients were selected according to the following criteria: a good general status, the absence of extra-abdominal lesions on preoperative imaging and the completeness of the cytoreductive surgery, which can only be appraised at laparotomy. In the literature, median survival is 7 months for unselected patients with colorectal PC without surgical treatment [23]. This median survival increases to 12.6 months for selected patients (good general status and the absence of extra-abdominal lesions) treated with chemotherapy alone (5-Fu and leucovorin and second-line CPT-11) [23], and is probably close to 24 months for patients with a good status treated with a combination of the most recent compounds. Recently, we retrospectively and carefully selected in 5 cancer centers in France, 48 patients (9 to 10 per center), who would have been eligible for surgery plus IPCH, but who did not receive this new combined therapy but the usual one with different lines of systemic chemotherapy. All of them underwent a laparotomy and had potentially resectable PC. They received a median of 2.47 (range: 1–5) different lines of recent systemic chemotherapy regimens, including oxaliplatin and CPT-11. Median survival was 24.8 months (data not yet published). This good median survival rate can be interestingly compared with the median survival of 60.1 months that we obtained in similar patients but treated with IPCH plus systemic chemotherapy.

Third, the efficiency of IPCH with mitomycin C at 41°C over 90 min has already been proven in a randomized study in patients with colorectal tumors, but not with such compelling results [24]. It is interesting to note that mitomycin C is an antibiotic whose antitumor activity has been established for over 40 years. It was mainly used 20 years ago to treat carcinomas of the stomach and ovary, but not for colorectal cancer. Historically, Japanese surgeons were the first to develop the combination of surgery plus IPCH to treat gastric cancer [25, 26]. So, they logically administered mitomycin C intraperitoneally. However, during the following years, mitomycin C continued to be used during IPCH, despite a lack of evidence for its efficacy in non-gastric digestive cancers. 5-Fluorouracil, the most useful compound against colorectal cancers over the last ten years is not used during IPCH because its activity is limited to dividing cancer cells and drug dwelling time needs to be prolonged in order to be efficient. LOHP is a rapidly acting compound that is far more potent against colorectal cancer than mitomycin C, whose efficacy is impaired with hyperthermia, as is the case with all platinum-derived compounds. Used at a high dose (460 mg/m2) and at a high temperature (42°C) during IPCH, it is theoretically more efficient than the other conventional drugs at a lower temperature [17]. At this point in time, we are unable to determine whether the improved survival rate in our series can be attributed to the use of LOHP, or to the high temperature, or to the completeness of cytoreductive surgery or the learning curve. We feel that these four possible explanations taken together yielded such results. Two other parameters may also explain our survival results. First, there was no postoperative mortality in this series, which is unusual. Usually, our mortality rate approximates 5%, so we think that the absence of fatalities was simply due to chance in this study. Unfortunately, postoperative deaths have been observed after IPCH since closure of the trial. Second, 7 (32%) of the 22 patients who relapsed underwent curative repeat surgery, underlining an “aggressive” approach in these selected patients. In the future, better selection of candidates for IPCH, and the use of intraperitoneal multi-agent chemotherapy such as a combination of LOHP with irinotecan and 5-fluorouracil [27], rather than single-agent chemotherapy should allow further improvement of survival.

Finally, in our short series, no significant prognostic factor was found in these selected patients who were able to receive this combined treatment. Neither the extent of the PC, nor associated extra-abdominal metastases had a prognostic impact. This is partly due to the limited number of patients in this series, but it also means that these parameters do not have a very strong prognostic impact. This is consistent with the new concept of multimodality treatment for most solid tumors: to treat macroscopic disease with an ablative local treatment (as surgery), and to treat any remaining microscopic disease with efficient systemic chemotherapy whose efficiency has already been proven in one patient. This approach is effective in curing PC, but also multiple liver metastases associated with extra-hepatic lesions. In this respect, as we recently showed, the number of metastases is more important than their site [28].
In conclusion, this new treatment modality is only feasible for selected patients with PC yields a 5-year overall survival rate of 48.5%, with a median survival unprecedentedly attaining 60.1 months.

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