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), followed by intraoperative intraperitoneal chemohyperthermia (IPCH) to treat residual microscopic disease achieves 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 extraperitoneal 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 2 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 dosages 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 précédant 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 (complications requérant un 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 à 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.

Peritoneal carcinomatosis (PC) is one of the most common causes of incurability of intra-abdominal cancers. Surgery or chemotherapy alone are not able to cure these patients. However, a new therapeutic concept [1] involving treatment of macroscopic PC with complete cytoreductive surgery and residual microscopic PC with intraperitoneal chemohyperthermia (IPCH) has already led to definitive cure of some cases of PC [2-4]. Complete cytoreductive surgery is necessary because experimental studies demonstrated that drug penetration only reaches a few cell layers below the tumor surface [5]. Intraperitoneal (i.p.) chemotherapy must be immediate, avoiding trapping residual tumor cells in postoperative fibrin adhesions [6, 7]. IPCH allows a high local concentration of antineoplastic agents [8, 9], and hyperthermia enhances their cytotoxicity [8, 9]. The cytoto-
xicy 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 platinas 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/m^2 of LOHP in 2 L/m^2 of iso-osmotic 5 % dextrose, at 42-44 °C over 30 minutes, given intraoperatively after an intravenous (i.v.) infusion of 5-fluorouracil (400 mg/m^2) with leucovorin (20 mg/m^2), was well tolerated. It was also interesting from a pharmacological point of view, with intratumor penetration 17.8-fold higher than in unbuffered tissue.

In 2004, we published the preliminary results of a study 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 colorectum 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/m^2) 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 with LOHP. 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 oncologic 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.

#### Intraoperative data

The preoperative work-up included a clinical rectal examination to evaluate Douglas pouch involvement, a CT scan of the thorax and abdomen, 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 oncologic 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).

### Intraoperative data

Intraoperative data are reported in table I (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). Before 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...
(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 (hepatic or perirenal), nor the extent of the PC (peritoneal index), nor the presence of (resected) metastases inside the liver, spleen or ovary. These parameters do not have a very strong impact, as we recently showed, the number of metastases is partly due to the limited number of patients in this series, but it is an additional factor that must be taken into account.

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].

![Overall and disease-free survival rates of 30 patients with colorectal carcinomatosis treated with maximal cytoreductive surgery and intra-peritoneal chemohyperthermia with oxaliplatin.](image-url)
In conclusion, this new treatment modality which 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.

REFERENCES

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