ABDOMINAL CANCER WITH PERITONEAL CARCINOMATOSIS TREATED BY PERITONECTOMY PROCEDURE AND INTRAPERITONEAL CHEMOHYPERTHERMIA

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РАК ОРГАНОВ БРЮШНОЙ ПОЛОСТИ С КАРЦИНОМАТОЗОМ БРЮШИНЫ: ЛЕЧЕНИЕ МЕТОДОМ ПЕРИТОНЭКТОМИИ И ВНУТРИБРЮШИННОЙ ТЕРМОХИМИОТЕРАПИИ

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The aim of this study was to estimate the results of a phase I–II prospective study in which peritoneal carcinomatosis was managed with Peritonectomy Procedure (PP) associated with Intraperitoneal Chemohyperthermia (IPCH).
Methods: Twenty two patients were included for peritoneal carcinomatosis from colorectal cancer (14), ovarian cancer (2), peritoneal malignant mesothelioma (2), gallblader cancer (1), gastric cancer (1), appendiceal cancer (1) and peritoneal pseudomyxoma (1). Peritoneal carcinomatosis was mainly advanced disease (19 stage 3 and 4, 2 stage 2, 1 stage 1). All the patients underwent surgical resection of their primary tumor with PP as described by Sugarbaker and IPCH (with mitomycine C, cisplatinium or both). IPCH used in this study was a "closed sterile circuit" device with inflow temperatures ranging from 46 to 48°C. IPCH was performed on the same day as PP (12/22) or delayed (10/22).
Results: Significant down staging of peritoneal carcinomatosis was achieved for 18 patients. One patient died postoperatively while morbidity rate was 7/22 (2 long postoperative ileus, 2 grade 3 leucopenia, 2 anastomotic leakage and 1 biliary fistula).
Conclusions: PP combined with immediate IPCH is an aggressive treatment. Despite a high morbidity, this association appears to be an effective therapy in peritoneal carcinomatosis. Larger phase III studies are now needed to demonstrate its efficacy on long-term survival.
Key Words: **peritonectomy, intraperitoneal chemohyperthermia, peritoneal carcinomatosis, digestive cancer.**

Сообщены результаты первой-второй фазы клинической проверки методов лечения больных с карциноматозом брюшины с помощью перитонэктомии (ПЭ) в сочетании с внутрибрюшинной термохимиотерапией (ВТХТ). Из 22 пациентов с карциноматозом брюшины, включенных в исследование, у 14 был рак толстой или прямой кишки, у 2 — рак яичников, у 2 — злокачественная мезотелиома брюшной полости, у 1 — рак желчного пузыря, у 1 — рак желудка, у 1 — рак аппендикса и у 1 — псевдомиксома. У большинства пациентов диагностирована далеко зашедшая стадия карциноматоза брюшины (у 19 — 3–4 стадия, у 2 — 2 стадия и у 1 — 1). Всем больным выполнена хирургическая резекция первичной опухоли с ПЭ по Шугербейкеру и ВТХТ (с митомицином С, цисплатином или обоими препаратами). ВТХТ осуществляли с помощью прибора, обеспечивающего "замкнутый стерильный контур" с температурой на входе от 46 до 48°С. ВТХТ проводили в тот же день, что и ПЭ (у 12 из 22 больных) или позднее (у 10 из 22). У 18 больных наблюдали снижение стадии карциноматоза брюшины. Один больной умер в послеоперационный период. Осложнения наблюдались у 7 из 22 больных (у 2 — кишечная непроходимость в отдаленный послеоперационный период, у 2 — лейкопения третьей степени, у 2 — несостоятельность анастомоза и у 1 — желчный свищ).
Выводы. Резекция брюшины в сочетании с ВТХТ, проведенной непосредственно после ПЭ, является агрессивным методом лечения. Несмотря на высокую частоту осложнений, это сочетание представляет собой эффективный метод лечения больных с карциноматозом брюшины. Необходимо проведение третьей фазы клинической проверки для решения вопроса о выживаемости больных.
Ключевые слова: **перитонэктомия, карциноматоз брюшины, рак органов пищеварения.**

Peritoneal carcinomatosis (PC) is a common evolution of digestive cancer (48% of the gastric cancer with serosal erosion [1]), and is the terminal stage of the disease as most of the patients with PC are to die within 6 months [2]. During the last decade, there has been a renewed interest in peritoneal carcinomatosis, and new aggressive therapeutic approaches have been

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proposed and are currently under evaluation. We have been using Intraperitoneal Chemohyperthermia (IPCH) since 1989 in our department [3] and we previously reported from phase I–II and III studies that IPCH was a safe and reliable procedure to treat peritoneal carcinomatosis from digestive origin [4]. From our experience, the best efficacy of IPCH was achieved for stage 1 and 2 peritoneal carcinomatosis (Table 1) while stage 3 and 4 did not benefit from IPCH [5].

Table 1. Peritoneal carcinomatosis staging

Stage	Peritoneal carcinomatosis description
0	No macroscopic disease
1	Malignant granulations less than 5 mm in diameter Localized in one part of the abdomen
2	Malignant granulations less than 5 mm in diameter Diffuse to the whole abdomen
3	Malignant granulations 5 mm to 2 cm in diameter
4	Large malignant cakes (more than 2 cm diameter)

In 1995, peritonectomy procedure (PP) was described as a new possible aggressive surgical approach for peritoneal carcinomatosis [6]. We decided to perform PP to down stage peritoneal carcinomatosis and we conducted a phase I–II study to evaluate the feasability and the tolerance of the combination of PP and IPCH in peritoneal carcinomatosis.

PATIENTS AND METHODS

Type of study. An open, non randomized, monocentric phase I–II study was designed, located in the Surgical Department of Centre Hospitalo–Universitaire Lyon–Sud. It was initiated in January 1997 and closed in January 1999.

Inclusion criteria. a) age between 18 and 75 years, b) ECOG index = 0 or 1, c) peritoneal carcinomatosis from digestive or ovarian origin, d) no extra abdominal metastasis, e) no intravenous chemotherapy administration 1 month prior to the inclusion, f) normal white blood cell count, g) no previous abdominal radiation therapy, and h) signed informed consent.

Exclusion criteria. a) thoracic metastasis on preoperative CT scan, b) brain metastasis on preoperative CT scan, c) patient with abnormal preoperative cardiac ultrasonography, and d) patient with renal insufficiency.

Type of peritonectomy. The peritonectomy procedure described by Sugarbaker [4] was used through a median laparotomy (from xyphoid to pubis). Peritonectomies were performed by 2 senior surgeons working together. Peritonectomies were adapted to the location of the malignant granulations as guided by the surgeons' exploration and by extemporaneous biopsies (no systematic extensive peritonectomies were performed). Locations of peritonectomy performed were such as follows: 1) right diaphragmatic cupula, 2) left diaphragmatic cupula, 3) great omentum, 4) lesser omentum, 5) omental bursa, 6) right colon gutter, 7) left colon gutter, 8) Douglas' pouch, 9) mesenteric peritoneum (mesenteric peritoneum was not removed but malignant granulations located on it were destroyed by electrosurgical fulguration) and 10) Glisson's capsule.

Type of IPCH. At the end of the surgical procedure, or during the 21 postoperative days, an IPCH session was carried out. Under general anesthesia and general hypothermia (32°C), two inflow drainages were inserted under left and right diaphragmatic cupula (30 French silicone drainage, William Harvey, Bard Cardiopulmonary Division, USA) while a third drainage (outflow drainage) was inserted in the Douglas' pouch (32 French). Thermic probes (Mallinckrodt SA and Cair SA, Lozanne, France) were also inserted within the abdominal cavity (behind liver pedicula and nearby the 1st jejunal loop). Other thermic probes were set up outside the abdominal cavity: a) on the inflow and outflow drainages (8 cm from the skin), b) inside the bladder within a Foley catheter. Laparotomy was then closed and inflow and outflow drainages were connected to a closed sterile circuit in which a 4 to 6 liter perfusate (Travenol laboratory, Norfolk, England) was circulated by the means of an electromagnetic pump at a flow rate of 500 ml/min. The closed sterile circuit was heated by the mean of a thermal exchanger (Dideco, France) connected to a heating circuit. Intra and extra abdominal temperatures were connected to a thermic reader (Cair SA, Lozanne, France) and monitored every 10 min (Fig. 1). IPCH was performed during 90 min with close monitoring of respiratory and haemodynamic parameters at inflow temperatures ranging between 46 and 48°C.

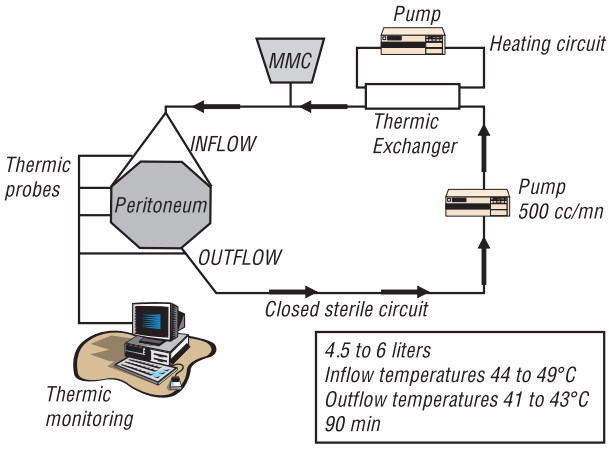

Fig. 1. IPCH procedure

Type of intraperitoneal chemotherapy. For peritoneal carcinomatosis from digestive origin, mitomycine C was used at the dose of 0.7 mg/kg (maximum dose of 60 mg). For peritoneal carcinomatosis from ovarian origin, cisplatinium was used at the dose of 1 mg/kg (maximum dose of 80 mg). For peritoneal carcinomatosis from peritoneal malignant mesothelioma or peritoneal pseudomyxoma, mitomycine C and cisplatinium were intraperitonealy associated at the dose of 0.5 mg/kg and 0.7 mg/kg respectively. Mitomycine C and/or cisplatinium were inserted in the peritoneal dialysis liquid at the beginning of IPCH.

Patients. Twenty two patients with peritoneal carcinomatosis were included in the present study:

10 males and 12 females, mean age 45.7 years, (SD = 13.7), ranging from 26 to 73 years. A great number of selection factors operated before and after referral and strongly influenced the composition of this patient population: these treatments were employed only in a small subset of patients with peritoneal carcinomatosis and during the period of the study 138 patients with peritoneal carcinomatosis were refered to our department. Primary tumors were right colon cancer (8), left colon cancer (6), ovarian cancer (2), peritoneal malignant mesothelioma (2), gallbladder cancer (1), gastric cancer (1), appendiceal cancer (1), peritoneal pseudomyxoma (1). For 10 patients, peritoneal carcinomatosis was synchronous and diagnosed at the time of the primary tumor diagnosis: for 12 patients, peritoneal carcinomatosis was diagnosed during the follow up of a known and already treated primary malignancy (10/12 received systemic chemotherapy treatments before being included in the present study). Details on peritoneal carcinomatosis, pathologic differentiation and initial pTNM staging are underlined in Table 2. Surgical

Table 2. PTNM staging, differentiation and peritoneal carcinomatosis staging

PTNM	PT2 = 1 PT3 = 10 PT4 = 8	PNO = 1 PN+ = 18
Differentiation	WD = 5 MD = 8 PD = 6	
Peritoneal carcinomatosis staging	Stage 1 = 1 Stage 2 = 2 Stage 3 = 5 Stage 4 = 14	

Malignant mesothelioma and peritoneal pseudomyxoma excluded from pTNM and differentiation. WD — well differentiated, MD — Moderately differentiated, PD — Poorly differentiated

resection consisted in 9 right colectomies, 3 left colectomies, 2 subtotal colectomies, 17 small bowell resections, 3 liver metastasectomies, 4 bilateral oophorectomies, 1 total gastrectomy, 2 partial gastrectomies, 4 hysterectomies, 9 cholecystectomies, 5 splenectomies, 1 left pancreatectomy and 3 retroperitoneal lymphadenectomies: thirty eight digestive anastomosis were so performed. Details on PP are underlined in Table 3. Regarding IPCH treatments, 12 courses were performed the same day as the surgical resection (beginning of the series) and 10 courses were delayed (2 on the 8th postoperative day, 5 on the 15th postoperative day and 3 on the 21st postoperative day).

Patients follow up. All the patients included in the present study were postoperatively transferred to an intensive care unit for 24 hours and then referred in the surgical department. Twelve of the included patients received palliative systemic chemotherapy courses during their follow up (5–fluorouracil, oxaliplatinium and/or cisplatinium). Clinical, biologic and radiologic follow up of the patients were done monthly after they discharged from the surgical department.

Stastistical analysis. Data were captured on Statview software (Abacus Inc. Berkeley, USA). Data are expressed as mean, standard deviation (SD) and range. Survival rates are calculated according to the Kaplan–Meier method.

Table 3. Details on peritonectomy procedures

Location of peritonectomy	Number
Omentectomy	20
Right abdominal gutter	14
Left abdominal gutter	11
Douglas' pouch	11
Right diaphragmatic cupula	10
Left diaphragmatic cupula	5
Omental bursa	3
Lesser omentum	4
Mesenteric fulguration	16
Glissonectomy	1

RESULTS

No peroperative death occured. Duration of surgery was 6 to 9 h (excluding the duration of IPCH treatment). Among the 19 patients with stage 3 and 4 peritoneal carcinomatosis (i.e. malignant granulations more than 5 mm in diameter) it was possible to reduce the peritoneal tumor volume to stage 0, 1 or 2 (less than 5 mm in diameter) for 16 patients. Results of peritoneal carcinomatosis down staging are underlined in Table 4.

Table 4. Results of peritonectomy procedure (PP) on peritoneal carcinomatosis (PC) down staging

Results	Primary tumor	Initial PC staging	Post PP PC staging	Survival (months)	Status
Residual peritoneal tumors less than 5 mm in diameter	Gallblader	4	2	2	DFR
	Left colon	4	2	5	DFR
	Right colon	3	2	12	DFR
	Right colon	3	1	14	DFR
	Right colon	4	1	11	DFR
	Right colon	4	0	4.5	AND
	Stomach	3	2	5	AND
	Ovary	4	2	6	AND
	Right colon	4	1	7	AND
	Mesothelioma	4	1	16	APD
	Right colon	3	2	12	AND
	Ovary	4	2	14	AND
	Left colon	2	1	19	AND
	Left colon	4	2	20	AND
	Right colon	2	0	26	AND
	Left colon	4	2	32	DFR
	Pseudomyxoma	4	0	3	AND
	Left colon	3	2	1	AND
	Appendiceal	1	0	6	AND
Residual peritoneal tumors more than 5 mm in diameter	Left colon	4	3	/	POD
	Right colon	4	3	8	DFR
	Mesothelioma	4	3	1	AND

DFR — Died from recurrence, AND — Alive with no disease, APD — Alive with progressive disease, POD — Postoperative death

One patient (4%) died on the 27th postoperative day from peritonitis and septicaemia (massive leakage on colorectal anastomosis). Postoperative morbidity was 7/22 (32%): 2 prolonged postoperative ileus (up to 10 days without re–operation necessity), 1 jejunal fistula re–operated on on the 15th postoperative day, 1 transverse colon fistula (observed on the 19th postoperative day and medically treated), 2 grade 3 leucopenia (from the 5th postoperative day up to the 20th) and 1 biliary fistula (observed on the 2nd postoperative day and medically treated). Morbidity rates were 2/10

in the group of patients with delayed IPCH and 4/12 in the group of patients with IPCH performed on the same day as peritonectomy. Mean hospitalisation duration was 15.1 days (SD = 8.3, range 6–40 days).

Up to now, mean follow up for these 22 patients is 9 months. One patient died in the postoperative period. Seven patients died from evolution or recurrence. One patient is alive with progressive disease at 16 months and 13 patients are alive with no evidence of disease (Fig. 2).

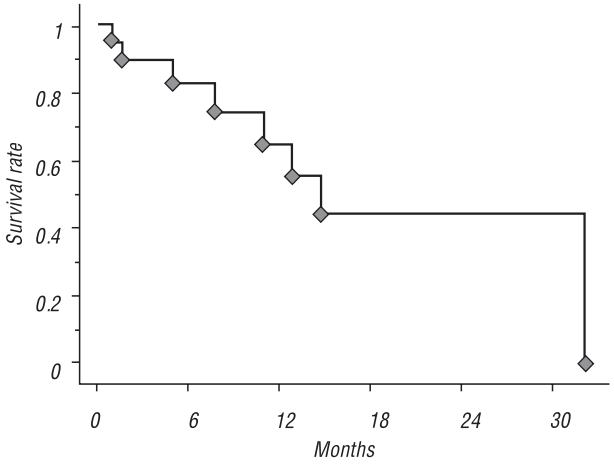

Fig. 2. Overall survival rate of patients treated by peritonectomy procedure combined with IPCH (Kaplan—Meier method)

DISCUSSION

Peritoneal carcinomatosis (PC) from colorectal malignancy always has been regarded as a lethal clinical condition and as a situation only to be palliated [2]. From the last decade, new possible aggressive therapies have been reported for peritoneal carcinomatosis treatment as intraperitoneal chemohyperthermia, immediate intraperitoneal postoperative chemotherapy and peritonectomy procedures [5, 7–10]. Intraperitoneal chemohyperthermia has been safely performed in patients with various intraabdominal malignancies. Hyperthermia, which can enhance the cytocidal effect [11], the submesothelial drug–penetration distance and the intracellular drug concentration, when combined with chemotherapy [12] has been tried as a treatment option for PC. Mitomycine C and cisplatinium are commonly used chemotherapeutic agents in combination with hyperthermia because it represents a marked pharmacokinetic advantage with intraperitoneal administration [5, 13–15].

The preliminary results showed that IPCH was effective for the small nodular type of peritoneal dissemination with diameter less than 5 mm (43% at 3 years in gastric cancer for stage 0, 1 and 2) but not for the large nodular type or diffuse infiltrating type (0% at 12 months for stage 3 and 4) [5]. Such preliminary results seem logical taking into account that thermal and drug penetrations are limited to 2 to 3 mm in depth [16]. Pharmacokinetics study performed during IPCH courses clearly demonstrated that drug absorption was important in the superficial layer of peritoneal tumors and that drug penetration did not exist in the central part of large and bulky tumors [16]. Theoretically, the cytoreductive approach by a surgical down staging of peritoneal carcinomatosis, may lead to a better efficacy of IPCH.

Peritonectomy procedures in digestive cancers is a new concept first described by Sugarbaker in 1995 [6]. Because residual tumor burden is minimal just after peritonectomy, intraperitoneal chemotherapy with or without hyperthermia may have the most powerful effects on the residual cancer cells. However Sugarbaker [17], in 181 appendiceal and colorectal cancers, treated by peritonectomy procedures with intraperitoneal chemotherapy reported 3 postoperative deaths and 21 postoperative bowel perforations or anastomotic leakages. Elias [18], in a phase II study including 54 peritoneal carcinomatosis from digestive origin, treated by peritonectomy procedures with immediate intraperitoneal postoperative chemotherapy reported a 61% morbidity rate. It was concluded that morbidity rates were highly correlated with the extension of peritonectomy and with the number of anastomosis performed [18]. As far as these aggressive treatment results are concerned, morbidity and mortality rates would appear as important ones. Moreover, it is to be underlined that the included patients from Sugarbaker and Elias' series (as well as our own patients) were strictly selected (young patients in good general status, no previous abdominal radiation therapy, no extra abdominal metastasis, no renal insufficiency, acceptable cardiac function, no systemic chemotherapy administration 1 month prior to the inclusion). It is also to be underlined that 10 of our 22 IPCH treatments were delayed from the peritonectomy procedures. Moreover, the dose rate of chemotherapy decreased: using IPCH alone, mitomycine C was used at a dose of 1 mg/kg but we believe that peritonectomy reduces the impact of the peritoneal barreer resulting in higher drug absorption in serum: new pharmacokinetic studies are currently ongoing in our department to evaluate the difference of drug absorption between IPCH alone and IPCH associated with PP.

Regarding the peritonectomy procedures, we decided to use adapted peritonectomy guided by the location of malignant granulations on the peritoneum: no systematic extensive peritonectomy was performed on area with no malignant granulation. Only 3 patients of our series required an omental bursa exeresis which represents the most difficult peritonectomy according to Sugarbaker; one patient Glisson's capsule peritonectomy because of high hemmorhage risk. At least, one could be surprised by using such aggressive therapies in peritoneal carcinomatosis, but peritoneal carcinomatosis may be a metastatic situation similar to other metastatic sites in which aggressive approaches are now performed. The survival of patients and the effect of chemotherapy are inversely related to the residual tumor burden. Moreover, unexpected long term survivals (up to 5 years) have already been reported for patients with peritoneal carcinomatosis treated by IPCH alone

or combined with immediate postoperative intraperitoneal chemotherapy or with peritonectomy procedures [5, 9,18–21].

CONCLUSIONS

PP combined with IPCH appears to be an effective therapy. It allows a down staging of PC. The high morbidity leads us to strongly recommend a strict selection of patients and to delay IPCH 8 to 21 days after PP for patients with several digestive anastomosis. After this phase I–II study, we are going to evaluate this association on long-term survival in colon cancer with PC, in a phase III study.

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