

Cytoreductive Surgery Followed by Intra Peritoneal Hyperthermic Perfusion in the Treatment of Peritoneal Surface Malignancies: Morbidity and Mortality with Closed Abdomen Technique

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Aims: The purpose of this phase II study was to analyze the morbidity and mortality of cytoreductive surgery (CRS) + intraperitoneal hyperthermic perfusion (IPHP) in the treatment of peritoneal surface malignancies. **Patients and methods:** One hundred and sixty four patients (36 ovarian cancer, 32 abdominal sarcomatosis, 34 peritoneal mesothelioma, 36 pseudomyxoma peritonei, 12 gastric cancer, 8 colon adenocarcinoma and 8 from other origins) underwent 166 procedures. Two patients underwent the intervention twice due to disease relapse. The mean follow-up was 20.6 months (range: 0.4 – 91.3). The mean age was 52 years (range: 24-76). CRS was performed with peritonectomy procedures. IPHP through Closed abdominal technique was conducted with pre-heated (42.5°) perfusate containing cisplatin+mitomycin C or cisplatin+doxorubicin for 60/90 minutes. **Results:** grade 3/4 morbidity rate was 12.0%. Some frequent post-operative complications were intestinal fistulas (17), respiratory (5) and abdominal bleeding (4). Multivariate analysis with logistic regression model with the backward elimination method identified carcinomatosis extension (OR: 5.3, CI95%: 1.2–24.5) as the best predictor of morbidity grade 3/4. Four patients presented grade 3/4 toxicity. Operative mortality rate was 0.6%. **Conclusions:** CRS+ IPHP presented acceptable morbidity 3/4 toxicity and mortality rates what support the need to be tested in prospective phase III clinical trial.

Key Words: Peritonectomy, Intraperitoneal hyperthermic perfusion, Morbidity

The evolution of locoregional therapy in the last 2 decades has changed the paradigm that has supported the management of patients affected by peritoneal surface malignancies (PSM). Examples of diseases that spread mainly within peritoneal cavity are pseudomyxoma peritonei, ovarian cancer, colorectal cancer, abdominal sarcomatosis, gastric cancer and peritoneal mesothelioma. Results of a phase III trial have confirmed the superiority of cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) in the treatment of colon cancer patients over

other standard surgical and/or systemic antitumoral modalities (1). More prospective randomized trials are ongoing to test the efficacy of this treatment modality in other tumour types (2). Nevertheless, CRS+IPHP still suffers a broad range of variability, with no consensus in various technical aspects. Thus, we attempted to make a contribution to this debate providing results of phase II study in which we analysed the morbidity, toxicity and mortality of CRS followed by IPHP (closed abdominal technique) in the treatment of patients affected by PSM.

Patients and Methods

Patients' characteristics

All patients included in this study were treated under an institutionally approved protocol with informed consent. The eligibility requirements for treatment were as follows: histologically confirmed diagnosis of peritoneal carcinomatosis, age < 75 years, no distant metastasis, adequate renal, haematopoietic and liver functions and performance status (ECOG) 0, 1 or 2.

One hundred and sixty four patients (36 ovarian cancer, 32 abdominal sarcomatosis, 34 peritoneal mesothelioma, 36 pseudomyxoma peritonei, 12 gastric cancer, 8 colon adenocarcinoma and 8 from other origins) underwent 166 procedures. Two patients underwent the intervention twice due to disease relapse. There were 59 men and 105 women. The mean age was 52 years (range: 24-75). The mean body mass index was 25 (range: 15.9-40). One hundred twenty five (75%) cases presented performance status = 0.

Cytoreductive surgery

The techniques of cytoreductive surgery have been described previously (3). Briefly, the surgical procedure was carried out with one or more of the following steps, depending on disease extension: 1) greater omentectomy, right parietal peritonectomy ± right colon resection; 2) pelvic peritonectomy ± sigmoid colon resection ± hysterectomy; 3) lesser omentectomy and dissection of the duodenal-hepatic ligament ± antrectomy ± colectomy; 4) right upper quadrant peritonectomy with Glissonian's capsule; 5) left upper quadrant peritonectomy ± splenectomy; 6) other intestinal resection and/or abdominal mass resection. A ball-tip electro-surgical handpiece was used to dissect the tumour on peritoneal surfaces from normal tissue (4). The electro-surgery was used on pure cut at high voltage. The 2 mm ball-tip electrode was used for dissecting on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumour destruction is required, the 5 mm ball-tip can be used. All the patients who underwent intestinal resections received anastomoses just after the surgical phase, before the initiation of IPHP. The bowel anastomoses were hand-sewn, one-layer sutures. Low colorectal anastomoses were performed with an intraluminal stapler of 29-33 mm diameter. No patient underwent diverting ostomies. Cytoreduction was classified into 3 levels according to the number of procedures performed: level I - 1-2 procedures; level II - 3 or 4 procedures; level III - more than 5 procedures.

Peritoneal carcinomatosis was quantified according to Peritoneal Cancer Index (5). Residual disease after surgery was classified according to Sugarbaker criteria (5): cc-0: no residual disease; cc-1: minimal residual disease: 0-2.5mm; cc-2: residual disease 2.5mm-2.5 cm; cc-3: residual disease >2.5cm. Accordingly 143 (86%) patients were optimally cytoreduced (cc-0/1).

IPHP technique.

After cytoreduction, 4 silicone catheters were placed in the abdominal cavity; one in the right subphrenic cavity, one in the deep pelvis, one in the left subphrenic cavity and one in the superficial pelvic site cavity. In order to continuously monitor peritoneal temperature during IPHP, thermocouples were placed in the abdominal cavity. Following the closed abdomen technique, the skin was closed with a running suture. The catheters were then connected to the extra-corporeal circuit. A heart-lung pump forced the instillation of a polysaline perfusate (4-6 litres) containing cisplatin (cDDP, 25 mg/m²/l) plus mitomycin C (MMC, 3.3 mg/m²/l) or cisplatin (cDDP, 43 mg/l) plus doxorubicin (Dx, 15.25 mg/l) (6) into the abdominal cavity through the circuit, at mean flow of 600 ml/min. The mean doses of drugs administered were 218 mg (range: 100-300) for CDDP, 31 mg (range: 15-50) for MMC and 63 mg (range: 25-90) for Dx. A heat exchanger kept the perfusate at 44° C as it was being administered, so that the intracavitary perfusate was maintained at 42° C to 43° C. The IPHP lasted 60 to 90 minutes, on the basis of the drug schedule. Following perfusion, the perfusate was quickly drained and the abdomen closed after careful intracavitary inspection.

Study parameters

Dependent variables were classified in 3 groups: combined grade 3/4 morbidity, post-operative enteral complication (defined as anastomotic and/or bowel fistula) and combined grade 3/4 IPHP related toxicity. Grading of complications was performed according to the following criteria: G1: no complications, G2: minor complications, G3: major complications (requiring reoperation or Intensive care unit admission or interventional radiology and G4: in hospital mortality. Grading of toxicity was performed according to the WHO criteria. We considered only those unfavourable events occurring within the 28th day after the procedure.

Seventeen clinical independent variables were taken into the consideration for potential association with post-operative complications: histology of primary tumour, sex, performance status, age, body mass index, previous chemotherapy, employment of cis-

platin in the previous antineoplastic treatments, employment of doxorubicin in the previous antineoplastic treatments, previous radiotherapy, extension of carcinomatosis, performance of intestinal anastomoses, number of intestinal anastomoses, duration of the procedure, extension of the surgical procedure, completeness of cytoreduction, IPHP drug schedule and dose of cisplatin in the IPHP. Continuous variables were categorized in 2 classes adopting their median value as cut-off.

Follow-up and statistical analysis

In the postoperative period patients were assisted in an Intensive Care Unit, where they were evaluated daily with laboratory and instrumental exams. The mean length of intensive care Unit stay was 3 days and the mean hospitalization was 18 days. Long-term follow-up was carried out by physical examination, tumour markers (Ca125, CEA, CA19.9), thoracic and abdominal CT scan every 3 months in the first year and every 6 months, thereafter. The mean follow-up was 20.6 months (range: 0.4 – 91.3). Analysis of treatment-related toxicity was performed according to World Health Organisation criteria (7). A univariate analysis of each clinical variable was performed by Fisher's exact test or chi square test to determine a probability of association with each morbidity variable. A logistic regression model was used in a multivariate analysis to determine a correlation between clinical variables and morbidity variables. All clinical variables that presented a p -value < 0.10 were included in the model. The backward elimination method was employed to determine which clinical variables best predict the presence of morbidity. All statistical analysis were conducted by using SPSS for Windows Version 8.0.0.

Results

Morbidity and mortality

Combined grade 3/4 morbidity occurred in 20 cases (12.0%). Examples of post-operative complications (G1-4) were 17 intestinal fistulas, 9 fever, 5 pneumonia, 4 pleural effusion, 4 renal failure, 4 abdominal bleeding and 2 sepsis. Other complications were one case of pulmonary embolism, one case of cardiac arrest promptly reversed with no sequel, one case of pancreatic fistula and one case of bile leak. One patient died in the early post-operative period due to duodenal fistula and abdominal bleeding rendering an overall mortality rate of 0.6%.

After univariate analysis the following variables were proven to have a statistically significant correlation with morbidity grade 3/4: male sex ($p=0.01$), previous systemic chemotherapy ($p=0.03$), carcinomatosis extension ($p<<0.05$), duration of the procedure ($p=0.02$) and extension of the surgery ($p=0.01$). Multivariate analysis with logistic regression model was used and after the backward elimination method male sex and (OR: 2.73, CI95%: 0.98-7.56) and carcinomatosis extension (OR: 5.3, CI95%: 1.2–24.5) remained in the model. (table 1)

Toxicity

Four patients presented grade 3/4 toxicity. There were 7 cases of haematological toxicity (6 grade 2 and 1 grade 3), 7 cases with gastrointestinal toxicity (grade 2), 8 cases of nephrotoxicity (4 grade 2, 2 grade 3 and 2 grade 4).

Discussion

The locoregional treatment for PSM is attracting an increasing interest of scientific community. However, the procedure is time and work consuming. The institution of a program in PSM requires not only a highly specialized human resources but also complex technological facilities (8), in order to perform the CRS+IPHP safely, minimizing treatment related morbimortality and maximizing their results in terms of survival and quality of life. In this context the identification of risk factors for postoperative complications is one of major concern. As outlined in the table 1, only sex and extension of carcinomatosis remained in the model after multivariate analysis. However, sex presented borderline significance ($p=0.052$), and thus only the carcinomatosis extension could be considered the best predictor of morbidity grade 3/4 between the analysed variables.

Jacquet et al. conducted a study on 60 patients with peritoneal carcinomatosis from adenocarcinoma of the colon or appendix treated with CRS, IPHP with MMC followed by one cycle of early postoperative intraperitoneal 5-fluorouracil. They employed the closed abdominal modality for IPHP and after a multivariate analysis including 11 clinical variables, sex, intrabdominal temperature and duration of surgery were identified as the best predictor of major morbidity. Stephens et al. reported on 200 cases of peritoneal carcinomatosis treated with CRS+IPHP using the Coliseum technique. After a multivariate analysis they found that the number of peritonectomy procedures

and resections was the only variable significantly associated with the presence of major morbidity (Odds ratio=1.32, $p= .0002$). Our results differ from those reported in these studies in that our independent risk factor for morbidity was not a procedure dependent one. Several factors could explain this contrast such as differences between the cohorts concerning sex distributions, tumour type distributions, IPHP techniques, rendering the comparison of results somewhat problematic. The analysis performed in this study comprised only clinical and surgical variables related to the preoperative and intraoperative phases of the procedure. The search for risk factors for complications should be continued, analysing other aspects of locoregional therapy. One can raise the hypothesis that including anaesthesiologic and immediate postoperative parameters, concerning haemodynamic, respiratory and/or nutritional status, new independent risk factors could emerge.

Investigators have not achieved a consensus about opened or closed abdomen techniques of IPHP. Proponents of Coliseum technique (open abdominal) (9,10) claim better drug and heat distribution by continuous manipulation of the abdominal organs. Deficiencies were noted in the distribution of methylene blue dye with the closed technique, which, in its turn, was blamed for higher rate of complications (11). On the other hand, the closed technique permits an increase in the intrabdominal pressure that might lead to increased convection driven drug penetration of macromolecular agents such as TNF α inside the tumour (12,13,14). Moreover, Jacquet et al. reported on animal models that that intra-abdominal pressure of 20 and 30 mm Hg increased tissue uptake of doxorubicin in bladder, diaphragm and abdominal wall during the first 10 min of intraperitoneal administration (15). Furthermore, a recent study carried out by Gelhen et al. reported the morbimortality results on 216 procedures of intraperitoneal chemohyperthermia using closed abdominal technique. They observed a postoperative mortality rate of 3.2% and morbidity of 24.5% (16). Since up to date no prospective controlled clinical trial has been conducted addressing specifically the superiority of one technique over the other, the issue remains unclear with no striking difference between both in terms of operative morbidity.

Another technical variation of CRS+IPHP is the optimal timing for bowel anastomoses. They can be performed during the CRS just before the IPHP or after the completion of IPHP. Proponents of first alternative argue that delaying the anastomoses permits a better distribution of heat and drugs inside the peri-

toneal cavity, during the IPHP. In addition, they state that the risk of postoperative bowel complications can be diminished due to avoidance of potential adverse effects of heat and chemotherapy on the suture healing. On the other hand, others have proposed the second alternative supported by experimental and clinical evidence. In fact, the influence of chemotherapy on the suture healing depends on the type of drug. In animal studies, anastomotic healing can be impaired by intraperitoneal MMC but not by 5-fluorouracil, at normal temperature (17,18) or paclitaxel (19). Local hyperthermia in itself has no adverse effect on rat anastomotic healing (20). Moreover, there seems to be no increased morbidity, due to post-operative bowel fistula and/or anastomotic leak when anastomoses are constructed before the IPHP (21,22,23).

Thus, our low and acceptable morbidity, toxicity and mortality rates suggest that the CRS+IPHP performed with primary intestinal anastomoses, closed abdominal technique and no liberal indication of ostomies is safe, in contrast with the opinion of some authors (9). Although the present study was conducted in a large cohort of patients it suffers from the methodological limitation regarding the absence of control group. In this sense it is premature to defend categorically one technique against other(s) as any attempt to establish a technical guideline for CRS+IPHP on the basis of experimental and uncontrolled clinical evidences is condemned to fail.

Finally, the results of our study suggest that the procedure is safe, once performed by an experienced surgical team seems and it seems to depend on the patients' characteristics and not to the operation itself. A definitive clarification of open technical issues will be possible only by adequately designed prospective randomized trials.

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Table I - Univariate and multivariate analysis of clinical risk factors for combined grade 3/4 morbidity.

| Independent variables | Categories | Morbidity n y | OR (crude) | p value (c2) | OR (adjusted)*/ CI 95% | p value |
|--------------------------------------|-------------------------|------------------|---------------|--------------|------------------------------|----------------------|
| 1) Tumour histology PMP | not PMP 29 | 117 7 | 13 | 2.17 | 0.12 | |
| 2) Sex (m/f) | f m | 98 48 | 7 13 | 3.79 | 0.01 | 2.73 0.98 - 7.56 |
| 3) Performance Status (ECGO) | >1 0 | 33 113 | 8 12 | 0.44 | 0.09 | |
| 4) Age | >52 <52 | 69 77 | 10 10 | 0.90 | 0.81 | |
| 5) BMI | >25 >25 | 80 63 | 13 7 | 0.68 | 0.42 | |
| 6) Previous CHT | n y | 64 82 | 14 6 | 0.33 | 0.03 | |
| 7) Previous cDDP | n y | 98 48 | 15 5 | 0.68 | 0.48 | |
| 8) Previous Dx | n y | 115 31 | 18 2 | 0.41 | 0.24 | |
| 9) Previous RT | n y | 141 5 | 19 1 | 1.48 | 0.72 | |
| 10) Carcinomatosis extension | PCI<20 PCI>20 | 64 82 | 2 18 | 7.02 | 0.00 | 5.32 1.16 - 24.53 |
| 11) Anastomoses | n y | 76 70 | 6 14 | 2.53 | 0.06 | |
| 12) Number of anastomoses | <1 >1 | 103 43 | 13 7 | 1.29 | 0.61 | |
| 13) Procedure duration | >510 min <510 min | 56 90 | 13 7 | 0.34 | 0.02 | |
| 14) Extension of surgery | Levels 1 e 2 Level 3 | 101 45 | 8 12 | 3.37 | 0.01 | |
| 15) Completeness of cytoreduction | cc0/1 cc2/3 | 127 19 | 16 4 | 1.67 | 0.40 | |
| 16) IPHP drug schedule | CDDP+Dx CDDP+MMC | 93 53 | 12 8 | 1.17 | 0.75 | |
| 17) cDDP IPHP dose | <240 >240 | 71 75 | 6 14 | 2.21 | 0.12 | |

OR: odds ratio; PMP: pseudomyxoma peritonei; BMI: body mass index; CHT: chemotherapy; cDDP: cisplatin; Dx: doxorubicin; RT: radiotherapy; * logistic regression model with backward elimination method.

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