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ORIGINAL ARTICLE

Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy in the Treatment of Peritoneal Dissemination of Neoplasias: Preliminary Results with Closed Perfusion Technique

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ABSTRACT

OBJECTIVE: to describe preliminary results of cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in the treatment of peritoneal carcinomatosis from a brazilian single institution. MATERIALS AND METHODS: a short cohort study was carried out. 26 patients and 28 procedures were performed consecutively between March 2001 and June 2005. 17 patients (65.4%) were treated for pseudomyxoma peritonei, 4 patients had mesothelioma, 2 carcinomatosis from colorectal cancer origin, 2 from ovary cancer and 1 had peritoneal sarcomatosis. All cases were treated with closed perfusion technique. The Completeness of Cytoreduction Score was used to classify the radicality of the procedure and the NIH Commom Toxicity Criteria was used to classify the complications. RESULTS: CC0 and CC1 resections were achieved in 24 cases (85.7%). Grade 3 or 4 toxicity were observed in 5 cases (17.8%) and two patients died (7.1%). Severe complications were significant associated with the duration of surgery (more than 10 hours). CONCLUSION: this radical treatment of peritoneal carcinomatosis envolves high morbidity and mortality rates and must be conducted in referral centers with multiprofessional teams and carefully selection of patients.

Key words: Peritoneal neoplasms. Surgery. Chemotherapy. Hyperthermia, induced therapy.

INTRODUCTION

Controversial publications brought to light new perspectives in the treatment of patients with neoplasm peritoneal dissemination originating from different tumors. That is a group technically and emotionally difficult to manage, consequence of previous therapeutic failure with conventional treatments and from the fast and progressive declining quality of life.

Although some concepts for the practice of cytoreductive surgery associated to intraperitoneal chemotherapy have been established for the treatment of the appendix carcinoma with peritoneal dissemination, for pseudomyxoma peritonei, and for peritoneal mesothelioma, its role in the treatment of peritoneal dissemination originated from other neoplasias has not been defined.[1-4]

The cytoreductive surgery (CS) associated to the intraperitoneal hyperthermic chemotherapy (IPHC) has their principles based on the supposition that the surgery makes the peritoneal disease reduction to a microscopic or minimum condition possible and allows lysis of adhesion, creating conditions for a greater effectiveness of chemotherapeutic agents, potentiated by heat.

Different series have demonstrated encouraging results, with morbidity and mortality rates varying respectively from 0 to 39% and from 0 to 20% in patients with of peritoneal dissemination originating from

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different primary tumors, suggesting that the procedure can be safely performed in selected patients.[5,6] It is thought this therapeutic approach, for a select group of patients, is potentially able to provide an increase in the survival rates, with acceptable incidence of complications. In this paper, we report the results of AC Camargo Cancer Hospital -São Paulo initial experience with cytoreductive surgery associated to intraperitoneal hyperthermic chemotherapy with closed perfusion technique.

PATIENTS AND METHODS

PATIENTS CHARACTERISTICS

Patients with peritoneal dissemination originating from different primary tumors, after systematic evaluation for exclusion of extra-peritoneal disease, and signature of informed consent, received the proposed treatment through CS and IPHC. Between March 2001 and June 2005, 26 patients were consecutively treated at the Department of Pelvic Surgery of A.C. Camargo Cancer Hospital. Among this sample, 28 cytoreductive procedures with intraperitoneal hyperthermic chemotherapy were performed.

The median age was 48 years, range from 30 to 65. Seventeen patients were female and 9 were male. 17 patients (65.4%) were treated for pseudomyxoma peritonei. Amomg the others, 4 have mesothelioma, 2 carcinomatosis from colorectal cancer origin, 2 from ovary cancer and 1 had peritoneal sarcomatosis. 13 patients (50%) have previous multi-modality treatments.

CRITERIA FOR CLASSIFICATION

With the purpose of evaluate the extension of the peritoneal dissemination, we have applied the Peritoneal Cancer Index (PCI), except for pseudomyxoma patients. Briefly, PCI consists in the sum of lesions size indexes in 13 areas of the peritoneal cavity.[7-9] The criteriaa used to estimate the surgical cytoreduction was the cytoreduction score (CCS) (Table 1). Cytoreduction was characterized according to the removal of peritoneal implants, including the accomplishment of sectional or total peritonectomy, when necessary for the acquisition of complete cytoreduction, the resection of organs and/or macroscopically damaged structures.[2] In peritoneal disseminations originated from pseudomyxoma peritonei and peritoneal mesothelioma, the cytoreduction was considered excellent with the acquisition of CC_0 or CC_1. For peritoneal carcinomatosis from colorectal and ovary tumors, only cytoreduction CC_0 was considered optimal. In those cases where the macroscopic peritoneal dissemination was located, the cytoreductive surgery was only limited to its areas, since the purpose was to get resection CC_0 or CC_1. The NIH Common Toxicity Criteria was used to classify the complications.

Table 1- The Completeness of Cytoreduction Score (CCS)

Classification	Residual disease
CCS-0	No macroscopic residual disease
CCS-1	Nodules < 2,5mm
CCS-2	Nodules 2,5 – 25mm
CCS-3	Nodules > 25mm

STATISTICAL ANALYSIS

Data were prospectively collected. The database was set up in the program SPSS for Windows version 10.0. Simple frequencies of all variables were first analyzed. Association between variables was assessed by the qui-square or Fisher´s test and relative risk estimative.

TECHNIQUE DESCRIPTION

In all the patients, IPHC was performed by the closed perfusion technique, according to the following standardization: finished the cytoreduction stage, an infusion catheter 22FR and 3 drainage catheters 19FR are positioned through the abdominal wall, respectively one in pelvic cavity and two in the right and left subphrenic spaces. In the drainage route, we have used tubular multiperforated Jackson-Pratt drains or multiguttered Blake drains, which remained installed at the end of the surgery. Two or three thermometers are placed into the peritoneum, one into the pelvic cavity, one into the superior floor of the abdomen, and another close to the infusion route, besides the esophageal thermometer. Peritoneal cavity is temporarily closed by continuous suture with

2.0 nylon thread of the skin (noninvasive neoplasias) or of the aponeurosis (invasive neoplasias). Perfusion starts with chemotherapy solution, previously chosen according to the origin of the peritoneal dissemination. The perfusion equipment manufactured by the Braille Biomedical Company consists of a propeller roll that impels the chemotherapy solution through the infusion catheter and removes it through the suction drains, returning the solution to a reservoir. A heat exchanger coupled to the system maintains the solution temperature between 44ºC and 46ºC, so that perfusion is kept for 90 minutes with intraperitoneal temperature between 41ºC and 42ºC. At the end of the intra-operative perfusion, cavity is irrigated with physiologic solution and then anastomoses are made. The infusion catheter is substituted by a Tenckhoff catheter to initiate early postoperative intraperitoneal chemotherapy (EPIC). When subdiaphragmatic peritonectomy stage is carried out, it is advisable the ipsilateral pleural drainage (Figure 1).

RESULTS

Among patients with non-pseudomyxoma disease, the median PCI was 18 (2-26). CC0 and CC1 resections were achieved in 24 cases (85.7%). 4 (14.3%) cases had inadequate (CC2 or CC3) resections. The median surgery time was 11 hours (range from 6h45min to 17h). The median blood cell component perioperative transfusion was 1,5 unit (0-10) for red blood cells and 1,14 unit (0-8) for fresh frozen plasma, respectively. A significant decrease in plasmatic proteins levels was observed during the perioperative period. The serum albumin levels decrease to a median of 1.9g/dL (0.9 – 3.3). The trombin activity decreases to a median level of 55% (28 – 85). The median Intensive Care Unit stay were of 4 days (0-16). Total hospital stay were of 11 days (range from 5 to 41).

Among the 28 surgeries performed, grade 3 or 4 toxicity was observed in 5 cases (17.8%). Complications are shown in Table 2. We did not identify association between severe complications (grade 3 or 4) with the extent of surgery (visceral resection or not) or previous manipulation (large resections or biopsy

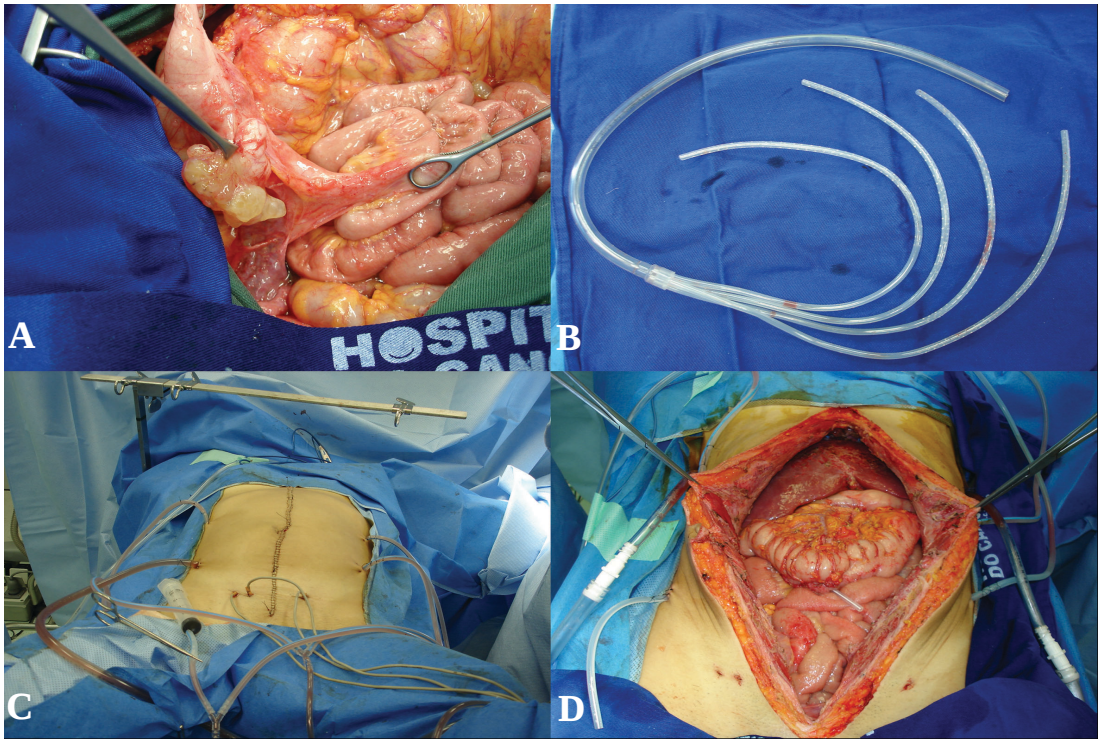

Figure 1 - A: Example of primary appendiceal malignancy. B: modified four-way catheter for trans-operative closed infusion. This catheter promotes a better distribution of the infusate through the peritoneal cavity. C: closed perfusion technique. D: open cavity after cytoreduction and perfusion. Note bilateral pleural drainage and the drains for postoperative intraperitoneal chemotherapy

procedures). We observed significant association between duration of surgery (more than 10 hours) and grade 3 or 4 toxicity (RR=1.56; 95% CI: 1.05 – 2.3; p=0.046).

The mortality rate was 7.1%. One patient died by late postoperative bleeding associated with coagulopathy and another by respiratory infection and sepsis. Patients status at the end of the analysis is expressed in Table 3.

Table 2- Morbidity rates

Toxicity grade	N (%)	Description (n)
0	10 (35.7)	
1	7 (25)	Pleural efusion (2), diarrhea (2), vomiting (2), ileus (2), nausea (2), urinary tract infection (1)
2	6 (21.4)	Pulmonar congestion (1), wound related pain (1), intestinal oclusion with conservative treatment (1), ileus (1), diarrhea (1), hepatititis (1)
3	3 (10.7)	Febrile neutropenia(1), hipotension(1),endocarditis(1)
4	2 (7.1%)	Intravascular coagulopathy(1), pulmonary infection (1)

Table 3- Patients status after 8.5 months median time follow up (1 to 48 months)

Status	Number of patients(%)
Alive without evidence of disease	16 (61.5)
Alive with recurrence	6 (23)
Dead from recurrence or treatment	4 (15.4)
Total	26 (100)

DISCUSSION

In spite of the development of new agents and chemotherapeutics combinations, the results of peritoneal dissemination treatment with systemic chemotherapy continue disappointing, with limited impact on survival.[10-13] For those reasons, an alternative therapeutic proposal, based on the combination of cytoreductive surgery and intraperitoneal hyperthermic chemotherapy has been evaluated.

To this moment, data are not enough to indicate the cytoreductive surgery associated IPHC as pattern conduct indiscriminately in the treatment of the peritoneal dissemination of neoplasias. The most important and difficult task is discerning selection of candidates to the procedure. In this sense, there are factors to be considered: primary tumor origin with its anatomopathological characteristics, the restaging indicating disease restricted to the peritoneal cavity, the peritoneal dissemination extent, the decision of the possibility of optimal and suboptimal cytoreduction, lack of therapeutic alternatives of confirmed effectiveness and patients clinical condition, among others.

We should consider that the pattern of peritoneal dissemination keeps strict correlation with primary tumor origin. Though, the disease natural history should be known, in order to avoid its indication without a logical rationale, what will invariably lead to clinical condition worsening without any benefit to the patient.

Careful patient selection candidates to the procedure is a fundamental task, since it is a new and aggressive method, associated with significant morbidity and mortality rates when it is badly indicated. For this reason, during initial phase, we have decided to indicate the procedure to patients with peritoneal pseudomyxoma and mesothelioma, where the impact of the cytoreduction on disease control is better established, due to the lack of effective therapeutic alternatives. With the growing number of publications on treatment of peritoneal dissemination originating from colorectal and ovary tumors, we extended the indication for some selected patients.

In current days, it can be considered that patients with peritoneal pseudomyxoma, noninvasive mesothelioma, and mucinous adenocarcinoma of the appendix presenting peritoneal dissemination are candidates to the surgical cytoreduction associated to IPHC, followed by EPIC. Those represent histological types with larger acquired experience, so that we can determine that this is the procedure of choice for the treatment of a representative fraction of the patients.

For peritoneal pseudomyxoma, because of the low invasion potential and metastasis, cytoreductive surgery associated to IPHC offers

good therapeutic results, with five-year survival rates up to 75% in different casuistics.[14-16] Among the 21 procedures performed for peritoneal pseudomyxoma, cytoreduction CC_0 or CC_1 was achieved in 18. Among these, 13 patients are asymptomatic without evidences of disease and 2 are asymptomatic with increase of CEA and/or suggestive recurrence by imaging techniques (median follow up time of 8.5 months, range from 1 to 48).

The malignant peritoneal mesothelioma is a locally aggressive disease with median survival of approximately 9 months when systemic treatment is instituted. Because of its tendency to remain confined to the peritoneal cavity, the cytoreductive surgery associated with IPHC has brought benefits for the control of this disease. Sugarbacker and cols. have reported a survival median of 67 months in 68 patients treated in Washington Cancer Center applying this therapeutic modality.[17] National Institutes of Health in the USA has presented median survival of 92-month for 49 patients.[18] Some histological variants of peritoneal mesothelioma do not have invasive character and their prognoses are favorable.

In the colorectal cancer, the presence of hepatic and lung metastasis frequently limits the indication of cytoreductive surgeries associated with IPHC in the treatment of the peritoneal carcinomatosis. About 10% to 15% of the patients with colon cancer have peritoneal involvement at diagnosis. Among those submitted to curative resection, approximately 50% develop peritoneal recurrence. In 10% to 35% of the cases, it is admitted that the recurrence is limited to the peritoneum.[19-26] As function of the bad results of exclusive treatment with systemic chemotherapy, the cytoreductive surgery associated to different extensions of peritonectomy and combined with intraperitoneal chemotherapy in perioperative period has been disclosed in the last years. Several studies report the use of combined strategy for the treatment of carcinomatosis of colorectal origin, with 3-year survival rates ranging from 23% to 39%.[21-34] Theoretically speaking, the certification of extra-peritoneal dissemination represents a relative contraindication for extensive cytoreductive surgery associated with IPHC. Patient in advanced initial stage, characterized by the presence of lymphonodal or systemic metastasis, and patient with diffuse peritoneal carcinomatosis, with impossibility of resection R_0 or R_1, constitute a group of bad prognosis. As function of the morbidity and mortality rates, the procedure has restricted indication to patients with favorable clinical conditions.

In our series, those two patients with colorectal origin carcinomatosis were young, in good general state, without extra-peritoneal disease and with limited carcinomatosis, susceptible to complete cytoreduction, besides they have failed to the adjunct schemes with 5-FU and leucovorin.

In 2003, Verwaal et al.[35] published a randomized study comparing cytoreductive surgery and IPHC (experimental group) versus palliative surgery and systemic chemotherapy (conventional group) in patients with peritoneal carcinomatosis of colorectal origin. In median follow up of 21.6 months, the median survival was 12.6 months in conventional treatment group versus 22.3 months in experimental group (log-rank; p=0.032). Median survival rates were also significantly superior in the group submitted to macroscopically complete cytoreduction (R_0 or R_1), when compared to survival rates in the groups of limited cytoreduction (R2a and R2b) (p <0,0001). Glehen et al.[36] have reviewed a multicenter experience of 28 institutions in different countries. The evolution of 506 patients with peritoneal carcinomatosis of colorectal origin submitted to cytoreductive surgery and perioperative intraperitoneal chemotherapy (IPHC and/or early postoperative intraperitoneal chemotherapy) has been analyzed. Those data have shown an actual benefit of cytoreduction associated to intraperitoneal intra-operative chemotherapy followed by early postoperative intraperitoneal chemotherapy. Some variables were considered of prognostic value, among which it is noticeable the complete cytoreduction, the limited extension of carcinomatosis, the use of adjunct chemotherapy and age below 65. Lymphonodal commitment, the presence of hepatic metastasis and the degree of histological differentiation, with worse prognostic for patients with little differentiated or undifferentiated tumors, were considered adverse factors. Preoperative use of systemic chemotherapy was pointed as a harmful factor by delaying the intervention and, by lack

of effective response, hindering complete cytoreduction at the moment of the surgery. In median follow up of 53 months the median global survival was of 19.2 months. Complete cytoreduction group has shown average survival of 32,4 months versus 8.4 months for incomplete cytoreduction group (p<0,001). Three- and five-year survival rates were 39% and 19% respectively. For patients submitted to complete cytoreduction, five-year survival rate was 31%.

Shen et al.[37] have retrospectively evaluated the results of the cytoreductive surgery associated to IPHC with mitomycin C by the closed perfusion technique in 77 patients with peritoneal carcinomatosis of colorectal origin. One-, three-, and five-year global survival rates were 56%, 25%, and 17%, respectively. In a median follow up of 15 months, the median global survival was 16 months. Five-year survival rate for patients submitted to complete macroscopic resection (R_0 or R_1) was 34%, with median survival of 28 months.

The results for the treatment of the peritoneal carcinomatosis of colorectal origin with the association of cytoreductive surgery and IPHC have shown significant rate of median survival and about 20% to 30% of 5-year survival, creating the concept that favorable results justify aggressiveness of the treatment, particularly when considering that the isolated systemic chemotherapy does not provide long term survival.[35-37]

Sufficient information to validate adjunct systemic chemotherapy application after complete cytoreduction associated to perioperative intraperitoneal chemotherapy is not available yet. Although, with favorable results by using new drugs such as oxaliplatin and irinotecan in patients with metastatic colorectal cancer,[38-39] it is prudent to consider that patients submitted to incomplete resections and those that have other bad prognosis factors (lymphonodal and concomitant hepatic metastases) can benefit of complementary systemic chemotherapy. To date, in colorectal cancer, enough data are not available to indiscriminately indicate the procedure for peritoneal dissemination treatment, however evidences indicate a promising future.

Patients with ovary carcinoma, with high potential for peritoneal dissemination after classical surgery still die of peritoneal dissemination and ascitis, despite the good results obtained with systemic chemotherapy. The two patients of our sample with ovary cancer submitted to cytoreductive surgery and IPHC were initially staged as IIIC, not susceptible to optimal or suboptimal cytoreduction in the first intervention. Nevertheless, they have shown significant clinical response after systemic chemotherapy, presenting minimum residual peritoneal disease in the second intervention. Thus, in ovary cancer, the current tendency is to propose the procedure for patients who had presented complete pathological response after systemic chemotherapy or show minimum residual disease at the occasion of the second intervention.[40-41]

Overall, the main factors to be considered in the patient selection are: primary tumor anatomopathological characteristics; surgical history; restaging; peritoneal dissemination extent; evaluation of the possibility for maximum cytoreduction; clinical condition and lack of therapeutic alternatives with attested effectiveness.

In Brazil, technical and conceptual aspects need to be better disclosed. One should keep in mind that association of the cytoreductive surgery to IPHC is a procedure that requires appropriate medical/hospital structure, where multiprofissional performance of surgical oncologists, clinical oncologists, anesthesiologists, intensivists, physical therapists and nutritionists must be interactive in order to achieve therapeutic success with acceptable morbidity and mortality rates. For that, every professional in this team must be aware of the concepts and particularities of the peritoneal dissemination patients candidate to a great intervention and must minimize the morbidity and mortality rates from the learning curve.

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