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PERITONEAL METASTASES IN COLORECTAL CANCER

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ABSTRACT

Peritoneal carcinomatosis (PC) is a common evolution of cancer of the gastrointestinal tract, and has been traditionally regarded as a terminal disease with short median survival. During the last 20 years, due to its favourable oncologic results, a new loco-regional therapeutic approach, combining cytoreductive surgery with intra-operative intraperitoneal chemotherapy has achieved an important development. After liver metastatic disease, peritoneal carcinomatosis is the second most frequent cause of death in colorectal cancer patient is defined as a stage IV tumour which prognosis is the worst. The extent of peritoneal carcinomatosis is, however, difficult for assessment preoperatively, and precise evaluation is most often performed during surgical exploration. Cytoreductive surgery associated with chemotherapy for the treatment of peritoneal carcinomatosis should be performed in young patients with limited and resectable carcinomatosis, in specialized institutions involved in the management of peritoneal surface malignancies.

Key words: colorectal cancer, peritoneal carcinomatosis, cytoreductive surgery

INTRODUCTION

Peritoneal carcinomatosis (PC) is, liver metastatic disease, the second most frequent cause of death in patients with colorectal cancer (CRC). The peritoneal surface is involved in 10%-30% (1-3) of patients with CRC and in roughly 7%-8% (3,4) at the time of primary surgery, in 4%-19% of cases during follow-up after curative surgery, in up to 44% of patients with recurrent CRC who require relaparotomy, and in 40%-80% of patients who succumb to CRC (4). However, in the 25% of patients with metastatic disease, the peritoneal cavity seems to be the only site of diffusion even after extensive diagnostic investigations (5). Presently, this last group of patients is commonly classified and treated as stage IV CRC, and there is no published data that outlines the impact of new therapeutic regimens on survival (6) and therefore research into new therapeutic approaches is widely justifiable and favourable. The PC occurs by a sequence of events: the spreading of cancer cells in the peritoneal cavity, their adhesion to the mesothelial surface and the invasion of the subperitoneal space for proliferation and vascular neogenesis (7). The high incidence of tumour implantation on the peritoneal surface in CRC can occur by intraperitoneal tumour emboli as a result of serosal penetration, or can be the consequence of surgical management through leakage of the malignant cells from the lymphatic vessels or through their dissemination due to tumour trauma because of dissection, with subsequent fibrin entrapment and tumour promotion of the entrapped cells (8). We review the accessible literature for reports about treatment of peritoneal carcinomatosis in patients with diagnosed colorectal cancer. We searched the MEDLINE database with the followed keywords: Colorectal cancer; Peritoneal carcinomatosis; Cytoreductive surgery. We found 33 suitable articles which were reviewed and used for our study.

The three principal studies (2,3,9) dedicated to the natural history of peritoneal carcinomatosis from CRC confirmed a poor prognosis with a median survival ranging between 6 and 8mo and no 5-year survivors. Chu et al (2) reported, in a series of 100 patients with PC of nongynecologic tumours, a median survival of 6 mo. Sadeghi et al (3), in a multi-centre prospective study reported 118 patients with PC from CRC with amedian survival of 5.2mo. In a retrospective analysis (9) of 3019 patients with CRC, 13% of these presented carcinomatosis and had a median survival of 7 mo. Verwaal et al (10), in a phase II randomized controlled trial of 50 patients who were treated with systemic chemotherapy and palliative surgery obtained an overall median survival of 12.6 mo with a 2-year survival rate of 18% and a median time to disease progression of 7.6 mo.

Cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPEC)

As reported by Esquivel et al (6), in the light of a new aggressive approach based on the combination of CRS and IPEC, the story of peritoneal carcinomatosis can probably be rewritten like the story of colorectal liver metastases. In the 1930s, Meigs (11) was the first to advocate CRS followed by adjuvant radiother-

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apy in patients with ovarian cancer but with poor results. Subsequently Munnell (12) and Griffiths (13), between the 1960s and 1970s, demonstrated that better survival rates could be achieved by more extensive surgery and that the size of residual disease is the most important prognostic factor (11). In 1980s, Spratt. was the first to report, after an experimental study with hyperthermic peritoneal perfusion in dogs (14), the results of CRS followed by IPEC using thioTEPA in a patient with pseudomyxoma peritonei (15). After this first clinical report, Sugarbaker et al (16,17) finally in the 1990s proposed and improved CRS and perioperative intraperitoneal chemotherapy as a possible treatment, initially for peritoneal dissemination of the appendiceal neoplasms and diffuse malignant peritoneal mesothelioma (14) and successively, for patients with PC from various gastrointestinal tumours.This was based on the realization that PC is a form of locoregional cancer dissemination rather than a systemic spread of the disease. Perioperative intraperitoneal chemotherapy consists of the intraperitoneal administration of drugs in a large volume of fluid either during the operation or postoperatively (16). Intraperitoneal chemotherapy can increase local exposure of the peritoneal surface to pharmacologically active molecules, especially those of high molecular weight (Mitomycin C, 5-FU, Doxorubicin, Cisplatin, Paclitaxel and Gemcitabine) resulting in a more uniform distribution throughout the abdominal cavity (16). This treatment can also be performed under hyperthermicconditions. Hyperthermia, associated with intraperitoneal chemotherapy, presents several advantages; it has a direct cytotoxic effect and enhances the activity and penetration depth of many cytotoxic drugs (17-19). Because it is estimated that the optimal target of thermochemotherapy is limited to few millimetres, is mandatory to resect all the macroscopic disease (20). According to Sugarbaker, the peritoneum can be divided into six parts, so between one and six peritonectomy procedures may be required, including visceral and parietal peritonectomies (16). Subsequently, when the resection of the cancer is complete, some catheters and suction drains are placed through the abdominal wall to permit perfusion, with open or closed abdomen techniques or with peritoneal cavity expander or a semi-opened or semi-closed technique. Elias, in a phase II study, using Oxaliplatin after administration of 5-FU and Leucovorin iv before IPEC, reported no case of mortality, 40% morbidity and a 5-year overall survival of 48.5% (median survival 60.1 mo) with a 73% rate of recurrence at 14mo (20) In another study, the same author, in a retrospective comparison of IPEC with Oxaliplatin vs standard systemic chemotherapy, found thatmedian survival. rate of the IPEC group was significantly better than that of the other group (62.7 mo vs 23.9 mo) (20).

Survival after CRS and IPEC

In the last decade, an increasing number of prospective studies investigated the effectiveness of the CRS and IPEC in the management of PC of colorectal origin. Meigs et al. (11) were the first who in 2003 conducted a randomized controlled trial comparing the efficacy of CRS and IPEC with systemic chemotherapy and surgery. This trial clearly demonstrated longer survival in the combined treatment group with a median survival of 22.3 mo vs 12.6 mo obtained in the control arm. Subsequently, Jacquet et al (17) in 1998, in a multi-institutional registry study from 28 international treatment centres, showed that the median survival was 19 mo and 3-year survival was 39% after CRS and IPEC for 506 patients with colorectal peritoneal carcinomatosis. However at present, the clinical outcomes, in the literature, vary considerably: the median survival from12 to 32mo, with 1-year, 2-year, 3-year and when reported 5-year survival rates ranging from 65% to 90%, 25% to 60%, 18% to 47% and 17% to 30%, respectively (4). Univariate and multivariate analyses of most series of patients with PC of colorectal origin revealed several clinical, surgical and pathologic factors predictive of survival (4). Clinical characteristics that have been correlated, in univariate analyses with an improved survival, are female gender, younger age and good clinical performance status (4). Surgical factors that have been correlated with survival are the extent of carcinomatosis encountered at laparotomy, the completeness of resection, bowel obstruction, the presence of ascites and the presence and resection ofmetastatic disease to the liver (4). Finally, the pathologic factors that have been correlated with impaired survival include site of the primary tumour, poor tumour differentiation, signet cell histology and lymph node involvement. However, the results of multivariate analyses on the abovementioned clinicopathologic factorswere reported in 5 publications; in 4 of these, the extent of disease [measured by Peritoneal Cancer Index (PCI)] and the completeness of resection were the factors most related to treatment success and survival (4). Patients with localization in six or seven regions of the abdomen had a poor prognosis, with a median survival of 5.4 mo vs 29 mo in those with a lower number of regions affected (7). In a recent retrospective study, in 70 patients, da Silva and Sugarbaker demonstrated, by univariate analysis, that the patients with a PCI < 20 had a median survival of 41 mo compared with 16 mo for patients with PCI > 20 (P =0.004). Verwaal et al. (10), using their seven regions system, demonstrated that the survival benefit was low in patients with more than five regions involved, with a greater correlated morbidity. The completeness of resection was also linked to survival. Median survival following complete resection of all macroscopic disease varied from 17.8mo to 39.0mo, whereas the reported-year survival rates varied from 20% to 54% while median survival, after incomplete resection, resulted inmedian survival times of 12.5-24mo,with 5-year survival rates between 10% and 29%.Whenmacroscopic disease ofmore 5 mm in diameter had to be left behind, the reported median survival varied between 5 and 12mo and none of these patients survived for 5 years (4).

Morbidity and mortality after CRS and IPEC

CRS followed by IPEC carries a postoperative morbidity of 14% to 55% and a treatment-related mortality of 0% to 19%, which seem to be related to the extent of surgery as a function of peritoneal involvement rather than to the IPEC (4). Elias et all. (20) suggested that there is a learning curve asso-

ciated with the procedure for achieving an acceptable morbidity rate and Witkamp affirms that postoperative complications could be resolved favourably inmost cases with correct patient selection and adequate postoperative care (8).

CONCLUSION

Arecent international conference was convened and a consensus statement on the appropriate use of CRS and IPEC was developed and adopted by the Peritoneal Surface Malignancy Group in an attempt to standardize the indications and techniques for this treatment (6). However we retain, according with the conclusion of Griffiths in his recent review (13), that a large prospective randomized controlled trial is needed to compare long-term and progression free survival under best available systemic therapy with or without CRS and IPEC. The selection of the patients for the management of peritoneal carcinomatosis associating CRS and IPEC is based on two main directions. From one point of view, patients have to be able to support an aggressive treatment associating surgery and chemotherapy. Secondly, tumors have to be completely resectable. With regard to the high level of postoperative mortality and morbidity and the oncological results, these principles are particularly true for the treatment of peritoneal carcinomatosis. The selection of patients has to be strictly performed to improve the outcomes. CRS associated with IPEC for the treatment of peritoneal carcinomatosis should be performed for young patients with limited and resectable carcinomatosis, in specialized institutions involved in the management of peritoneal surface malignancies.

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