Current role of hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal carcinomatosis from colorectal cancer

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Abstract

Peritoneal carcinomatosis is one of the most common routes of dissemination of colorectal cancer (CRC). It is encountered in 7% of patients at primary surgery, while it develops in about 4% to 19% of patients after curative surgery and in up to 44% of patients with recurrent CRC. Peritoneal involvement from colorectal malignancies has been considered traditionally as a manifestation of terminal disease, due to limited response to conventional surgical and chemotherapeutic treatments. In the past few years the introduction of cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion has shown promising results in selected patients. Currently, the surgical management of peritoneal surface malignancies of colonic origin with this combined locoregional therapy has resulted in a significant improvement in survival of these patients. However, further controlled studies will help to standardize indications and the technique of this locoregional therapy in order to achieve an improvement of morbidity and mortality rates.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in western countries. Despite the improvement in its prognosis, recurrence following resection of CRC remains a substantial problem.

Peritoneal carcinomatosis (PC) is one of the most common routes of dissemination of CRC. It is encountered in 7% of patients at primary surgery, while it develops in about 4% to 19% of patients after curative surgery and in up to 44% of patients with recurrent CRC^[1,2].

In the past, PC from colorectal malignancies has been considered as a manifestation of terminal disease, due to limited response to conventional surgical and chemotherapeutic treatments^[3,4].

Sugarbaker^[5], one of the pioneers of treatment of this disease, has suggested that PC is a locoregional cancer spread as a result of a molecular crosstalk between cancer cells and host elements.

For this reason the only chance to achieve long term

survival in these patients is the eradication of microscopic residual disease.

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In 1980 Spratt *et al*^[6], after an experimental study with hyperthermic peritoneal perfusion in dogs, were first to clinically test cytoreductive surgery followed by hyperthermic intraperitoneal chemoperfusion (HIPEC) with thiotepa in a case of pseudomyxoma peritonei.

Later Sugarbaker *et al*^[7,8] introduced intraperitoneal chemotherapy as a new innovative therapeutic option for selected patients with PC.

This treatment is based on surgical cytoreduction and HIPEC. The underlying rationale of this combined approach is that on one hand an aggressive surgical approach combining visceral resection and peritonectomy procedures addresses the macroscopic disease, whereas HIPEC is aimed at residual microscopic disease^[9].

Drugs selected for intraperitoneal administration usually are hydrophilic and have large molecular size, so that they pass slowly through a peritoneal-plasma barrier and are therefore more effectively sequestered in the peritoneal cavity. Adding hyperthermia to intraperitoneal chemotherapy may increase the tumor response to cancer chemotherapy drugs by several mechanisms. Firstly, heat alone has a direct anti-tumor effect. Hyperthermia above 41°C induces selective cytotoxicity of malignant cells. Secondly, the cytotoxic effects of some chemotherapeutic agents (doxorubicin, platinum complexes, mitomycin C, melphalan, docetaxel, irinotecan and gemcitabine) are augmented by applying mild hyperthermia^[10].

This locoregional therapy provides an elevated and persistent drug concentration for the tumor, with a limited systemic concentration.

HIPEC with mitomycin C, cisplatin and doxorubicin or oxaliplatin has been used for gastrointestinal PC. Oxaliplatin has been used intraperitoneally in Europe for colorectal PC, as pioneered by Elias *et al*^[11]. This drug has a very low area under the curve ratio, which means that oxaliplatin is rapidly absorbed and does not require a long dwell time in the peritoneal cavity for maximal local-regional effect^[11].

However, the extent of intraperitoneal chemotherapy penetration into tumor nodules by passive diffusion is limited to a few cell layers. For this reason Elias *et al*^[11] first suggested that intraperitoneal oxaliplatin should be combined with intravenous 5-FU administered just before HIPEC (bidirectional intraoperative chemotherapy). By combining intraoperative intravenous and intraoperative intraperitoneal cancer chemotherapy a bidirectional diffusion gradient is created through the intermediate tissue layer which contains the cancer nodules. This offers opportunities for optimizing cancer chemotherapy delivery to the target peritoneal tumor nodules.

Nevertheless, further pharmacologic studies are needed to clarify the most efficient method of administration (continuous *vs* bolus *vs* repeated bolus), doses and choice of cancer chemotherapy drugs for this bidirectional approach.

RESULTS TO DATE IN TREATING COLORECTAL PC

Since the introduction of HIPEC, promising results have been reported by several groups in the treatment of PC^[12,13].

In all published series, the most important prognostic factors in predicting survival are the involvement of disease encountered at laparotomy (measured by peritoneal cancer index, PCI) and the completeness of resection^[2].

A retrospective analysis of prognostic factors in 71 patients treated by cytoreductive surgery plus HIPEC for PC from CRC reported a median survival of 41 mo in patients with a PCI < 20, while in cases with PCI > 20 the survival was 16 mo^[14].

When there is extension of disease to six or seven regions of abdomen patients have a poor prognosis, with a median survival of 5.4 mo *vs* 29 mo in patients with a lower number of regions affected^[14-16].

Glehen *et al*^[17], in a study of 523 patients with PC from CRC, have reported a survival of 32.4 mo in patients who had a complete cytoreduction, compared with 8.4 mo in patients in whom a radical cytoreductive surgery was not possible.

The morbidity rates reported after HIPEC combined with cytoreductive surgery range from 20% to 50% and mortality rates from 1% to 10%^[18,19].

The main morbidities associated with this advanced treatment are caused by complications of surgery and hematological toxic effects. The most frequent surgical complications include anastomotic leakage, intestinal perforation, pancreatitis, prolonged ileus, bile leak, intra-abdominal bleeding/sepsis, wound dehiscence, pulmonary embolism and renal failure.

Intra-abdominal sepsis and enteric fistulas often necessitate re-operation. Most of these complications can be attributed to the extensive surgery performed, especially when the patient has had multiple previous operations. This procedure on average may take up to 10-12 h with a median blood loss of 3-5 L, and necessitates blood transfusion, complex anesthetic management, intensive unit care, and re-operation. To add to the complexity, Sugarbaker stresses that the dosing of intraperitoneal chemotherapy often needs to be modified to keep the morbidity and mortality for these patients at 30% and 2%, respectively. He suggests using a one-third dose reduction in patients who have had prior extensive surgeries, extensive cytoreductive surgery, if multiple anastomoses needed to be performed, those who have had prior chemotherapy or radiation therapy, and those who are older than 65 years^[20].

Results of multivariate analyses have shown that the independent factors affecting morbidity are duration of

surgery, extent of carcinomatosis, the number of anastomoses performed, and sex^[21,22].

The advanced stage of neoplastic disease and immunodeficient status of patients previously subjected to chemotherapy were found to be important factors that probably contributed to the occurrence of septic complications after an extended surgical procedure.

Furthermore, there are several technical and procedural nuances, which mandate that only those who have considerable experience should perform these procedures. Indeed, both the cytoreductive surgery and the administration of HIPEC are technically demanding procedures for which learning curves exist.

In a study of 70 patients treated with HIPEC combined with cytoreductive surgery, Yan *et al*^[23] have reported a mortality of 4%, a moderate morbidity in 44% of patients and that 20% displayed severe morbidity; these workers suggested that there is a learning curve associated with this advanced treatment in order to achieve an acceptable morbidity rate. Smeenk *et al*^[24] observed that the peak of the learning curve, graded by the percentage of complete cytoreductions, was reached after approximately 130 procedures. Therefore, such a complex, aggressive modality can be a considerable drain on the resources of an institution in order to provide benefit for a small group of patients.

Recently, Elias *et al*^[25] reported a multi-institutional retrospective analysis of cytoreductive surgery and HIPEC for patients with PC from CRC. This investigation involved treatment of 523 patients over a 17-year period with almost 30% ($n = 152$) from a single institution whereas, importantly, 18 centers recorded fewer than 20 cases each. The purpose of their study was to evaluate the short and long-term efficacy of this combined approach and determine prognostic factors affecting outcome. The overall mortality was 3.3%, with 31% grade 3 to 4 morbidity, and 30.1 mo median survival. The risk of postoperative morbidity and mortality was significantly influenced by two factors: the peritoneal index (reflecting the peritoneal metastatic burden) and the center in which the treatment was performed (inexperienced centers were those with < 7 years of practice). The center experience was an independent predictor for achieving the important goal of complete cytoreductive surgery^[25].

Currently patients with CRC who develop peritoneal recurrence might benefit from cytoreductive surgery and HIPEC even in the presence of resectable liver metastasis^[15,19,26-29]. Because this treatment has been shown to be most effective in patients with absent or minimal residual disease, there might be a role for preventive HIPEC in patients at high risk of peritoneal tumor spread. In a study of 29 patients with CRC at high risk of peritoneal recurrence, PC not detected by preoperative imaging was present in 16 patients. In these cases, HIPEC resulted in a disease-free status in half of the patients after a median follow up of 27 mo^[30,31].

CONCLUSION

The clinical outcome after a diagnosis of PC has radical-

ly changed during the last two decades due to combined locoregional treatment. At the moment, HIPEC provides a promising therapeutic option for patients with PC from CRC. Patients who have minimal residual disease as a result of cytoreductive surgery are candidates for HIPEC. This approach has become an important part of CRC treatment and should become a standard modality for prevention and treatment of cancer that involves the peritoneal surface. The national health care systems of the Netherlands and France have approved this approach for colon carcinomatosis. In other countries in Europe, approval is given on a case-by-case basis.

In order to achieve maximum benefit, correct selection of the patients approved for submission to this procedure, a radical cytoreduction and an adequate learning curve are necessary.

However, further controlled studies will help to standardize indications and the technique of this locoregional therapy in order to achieve an improvement of morbidity and mortality rates.

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