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REVIEW ARTICLE

Peritoneal carcinomatosis 2011; it's about time for chemosurgery

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Summary

The aim of this article was to offer a review on the management of peritoneal carcinomatosis (PC) from cancers of different primary origins.

Peritoneal surface malignancies have been traditionally regarded as end-stage conditions amenable to merely palliative options, treated with systemic chemotherapy alone with very poor response and a median survival of less than 6 months.

The combination of aggressive cytoreductive surgery (CRS), involving peritonectomy procedures and multivisceral resections with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) to treat microscopic residual disease is a new concept. This method was established with several phase III studies in well selected patients with PC in whom sufficient cytoreduction could be achieved. Despite the need for more high quality phase III studies, there is now a consensus among many surgical teams around the world about the use of this new combination strategy as a standard of care in pseudomyxoma peritonei, peritoneal mesothelioma and colorectal cancer patients.

This review summarizes the current status and possible progress in the future.

Key words: colon cancer, gastric cancer, HIPEC, ovarian cancer, peritoneal carcinomatosis

Introduction

PC is associated with a poor prognosis and, once diagnosed, survival is generally less than 6 months [1,2].

PC is a common mode of spread and implantation of cancer cells in the peritoneal cavity resulting in malignant tissue deposits involving parietal peritoneum surfaces or the visceral peritoneum lining abdominal and pelvic organs. PC is a major cause of decline in patient's functional status and quality of life, presenting as pain, ascites and bowel obstruction.

In order to evaluate the rational for the management of PC it is important to understand the pathophysiology of the problem. Primary peritoneal neoplastic disease as primary carcinoma and mesothelioma are rare conditions. Metastasis to peritoneal cavity from ovarian, colorectal, gastric, pancreatic and appendiceal carcinoma are more common [3].

PC can present in the form of malignant ascites, multiple small tumor deposits in various parietal sites, mucin deposits in the case of pseudomyxoma peritonei or layers of tumor tissue enveloping or invading peritoneal surfaces or organs.

Pathophysiology of peritoneal tumor spreading

Ten to fifteen per cent of intraabdominal and intrapelvic tumors have already developed PC during initial diagnosis. PC is formed through a multistep process but pathophysiological and molecular mechanisms of formation of PC are generally unknown [4].

The "tumor rupture" theory was proposed as a most attractive model. According to this theory there is detachment of cancer cells from a tumor of digestive or gynecological origin which exfoliates from the serosal surface of the primary tumor intraperitoneal free tumor cells that may attach to distant peritoneal sites and invade into the subperitoneal space with invasion, proliferation and vascular neoangiogenesis [5-7]. Recent studies, and especially a study by Yonemura et al. [7], demonstrated some special anatomic particles such

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as lymphatic orifices and stomata which connect with many spots in the molecular pathogenesis of PC [7-10].

The "tumor rupture" theory is difficult to explain PC from low rectal cancers with no direct communication to the peritoneal cavity and also the incidence of PC in perforated and non-perforated colon cancer which is equal in both conditions [8,9].

Another theory concerning PC is the "secretion theory". According to this theory the peritoneal cavity is a hostile environment for cancer cells and acts as a barrier for cancer spread.

The extracellular or intracellular mucin secretion by cancer cells and the presence of nutritional and growth factors as a healing process after an operation should be able to modify the peritoneal environment from hostile to friendly area for growth of tumor deposits [10]. This "secretion theory" explains the pseudomyxoma peritonei mucin production and also explains in combination the "tumor rupture" the "tumor cell-entrapment phenomenon" as described by Sugarbaker [11] in which the process of PC can be made easier by the surgical manipulations.

Epidemiology of peritoneal surface malignancy

Primary peritoneal surface malignancies (PSMs) are rare tumors and include peritoneal mesothelioma and peritoneal carcinoma.

Secondary PSMs are more frequent and discovered during operations for gastric cancer (GC) in 10% of the cases and in colorectal cancer in 20% of the cases. Also 60-70% of patients with T_3 or T_4 gastric tumors and in more than 50% of cases of colon cancers develop PC in the first 3 years after curative resection [12,13]. In ovarian cancer about 50-70% will develop PC during follow-up [14].

Peritoneal mesothelioma is a rare tumor, more common in females, with an incidence in USA of 1.1 cases/100,000 population. There are 3 mesothelioma subtypes: epithelial, multicystic and biphasic [15]. Primary peritoneal carcinoma is a papillary carcinoma involving the peritoneal cavity in the absence of an obvious primary. Many investigators consider it as a variant of ovarian cancer, with 3 types: serous papillary, mixed epithelial, and malignant mixed Mullerian tumor and accounts for 7-14% of ovarian carcinomas [16].

Management approach against peritoneal surface malignancy

In the past the management of PSM with systemic chemotherapy alone demonstrated poor results and surgery played a palliative role to relieve intestinal obstruction [1]. The current treatment is conducted according to consensus statements based on case-control studies, well designed retrospective trials and few prospective phase II clinical trials [9,15,16].

The evidence for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

In traditional surgical oncology R0 resection remains the gold standard for successful treatment, but this is not applicable in the treatment of PSM. The principles of a new concept for resection of peritoneal surfaces and organs covered by tumor-bearing visceral peritoneum for the treatment of PSM contains cytoreductive surgery (CS) which is vital in improving overall survival. It is important to make clear that CS means peritonectomy procedures as described by Sugarbaker [17] and not debulking surgery.

Peritonectomy consists of two big surgical components, parietal and visceral, greater omentectomy, splenectomy cholecystectomy, resection of Piver capsule, partial gastrectomy, subtotal or total colectomy and resection of mesentery. Also stripping of the parietal and diaphragmatic peritoneum [1,2].

In order to determine the extent of intraperitoneal tumor volume, the most valuable scoring system is using the peritoneal cancer index (PCI), a combined numerical score of lesion size ($L_{5\text{-}0}$ to $L_{5\text{-}3}$) and tumor localization (region 0-13) [18].

After finishing the CS, it is important to determine the completeness of cytoreduction score (CCS) in which CCS_0 indicates no visible residual tumor, CCS_1 nodules < 2.5 mm, CCS_2 nodules > 2.5 mm and < 2.5 cm and CCS_3 nodules >5 cm [19].

However, surgery alone sometimes leaves microscopic disease, tumor cells become sequestered in avascular intraperitoneal adhesions, thus explaining the resistance to and the ineffectiveness of systemic chemotherapy [20].

Animal studies demonstrate that direct intraperitoneal chemotherapy produces higher tissue drug concentrations as compared to systemic intravenous administration, with a limited tissue penetration of 2-3 mm of the superficial layer.

This phenomenon is attributable to an anatomic-histological barrier, the peritoneal-plasma barrier, which permits the exposure of peritoneal surface to high local concentrations of cytotoxic agents, far in excess of systemically delivered agents, with prolonged periods and rapid tissue concentration in residual tumors depos-

its, but limited systemic absorption and toxicity [21,22].

When this method is combined with hyperthermic administration of a drug solution increased tissue penetration and cytotoxicity of the delivered cytotoxic agent is achieved. Hyperthermia itself is cytotoxic mainly through inhibition of functions essential to DNA replication, transcription and repair [23-25].

The clinical gains of these effects are the combined antitumor effect of heat and intraperitoneal administration of cytotoxic agents which form the basis for the current treatment of PSMs [25]. The combinatorial effect of hyperthermia (42.5° C) and local chemotherapy can eradicate residual disease up to 2.5 mm left in the peritoneal cavity after a complete CS.

After finishing CS, HIPEC is initiated. This maneuver offers 2 main advantages. (A): Distribution of cytotoxic drugs directly into the peritoneal cavity. HIPEC is performed either with open or closed techniques with one inflow and 3 outflow drainages which are placed in the small pelvis and subphrenically. The drugs are applied via the inflow drainages using a roller pump and a neat exchanger in a closed system that allows perfusate circulation. And (B): hyperthermia, which is monitored by sensors placed in the outflow catheters. The temperature should reach 42.5° C while the perfusion time ranges from 30-120 min, depending on the protocol and the drug used [26,27].

Patient selection

CS and HIPEC are commonly indicated for the treatment of PSMs if the patient is fit and can stand this extensive operation.

The contradictions are the following: 1) patients that are medically unfit to undergo the rigors of CS and HIPEC; 2) there is extraabdominal disease; 3) there are more than 3 liver metastases; 4) there is bulky retroperitoneal disease [28,29].

For these reasons a clear preoperative staging is necessary for such a treatment. The classical preoperative diagnostics, such as different tests and imaging procedures, may be helpful for revealing tumor dissemination in the different spaces of the peritoneal cavity, but they do not necessarily correlate with intraoperative PCI [2,30].

Laparoscopy for staging may be interesting in PSM patients for diagnosis and maybe for therapeutic purposes, but the latter possibility is limited due to incisions or scars from the initial operations [31,32]. This means that in the future it could be possible to perform CRS and HIPEC laparoscopically in early-stage peritoneal disease.

There is also the tumor volume factor which should be taken into account. For example, patients with PCI<20 qualify for CRS and HIPEC if the tumor is of colonic or ovarian origin, with PCI<10 if the tumor is GS, and for pseudomyxoma peritonei and for mesothelioma a PCI>20 is acceptable for CRS and HIPEC [1,2,33-35].

All these problems demonstrate the controversial criteria in patients with PC. For these reasons different consensuses for different organs establish the indications for each category.

For example the ovary consensus panel declares no absolute contraindications for CRS and HIPEC except heart failure and pulmonary dysfunction [35]. On the other hand, for colorectal cancer the PSM group defined the variables that increase the probability of complete cytoreduction in patients with PC of colonic origin (Table 1).

Gastric cancer: benefits and results of CRS and HIPEC, and future directions

GC is a pathophysiologically heterogeneous disease, spreading by way of lymphatics. For lymphatic and hematogeneous spread reasonably extended D_2 lymphadenectomy, regional radiotherapy and adjuvant chemotherapy have been proved effective, as demonstrated by large-scale international studies [36].

These trials also show the same pattern of recurrence in different sites, the most common being in the peritoneal cavity.

These findings reflect the fact that GC is a disease with easy intraabdominal spread, largely because free cancer cells in peritoneal washings could be detected in up to 24% of stage I_B and up to 40% in stages II and III [37]. Tumor cells spread by the mechanisms described above are entrapped within fibrin exudates which protect them from host defences.

Not only is it important in understanding the pathogenesis of both resection sites and peritoneal surface recurrence, but also in appreciation of the beneficial effects of adjuvant perioperative chemotherapy.

Table 1. Positive variables for complete cytoreduction in colorectal peritoneal carcinomatosis

ECOG performance status <2
No evidence of extra-abdominal disease
Up to 3 small resectable liver deposits
No evidence of biliary obstruction
No evidence of ureteral obstruction
No evidence of bowel obstruction at more than one site
No evidence of gross disease in the mesentery of the small bowel
No evidence of bulky disease in gastrohepatic ligament

Surgical treatment is the main treatment of GC.

Adjuvant systemic chemotherapy following surgery with curative intent is the only change for reduction of disease recurrence and related mortality, but in a meta-analysis of 14 randomised trials evaluating the role of adjuvant chemotherapy combining curative surgery vs. surgery alone, only a small survival advantage was found in the arm of systemic chemotherapy [38].

The MAGIC trial, a neoadjuvant regimen with 3-drug combination, was shown in a prospective randomized trial effective to increase the 5-year survival rate (36 vs. 23%) as compared to surgery alone [39].

The results of trials with systemic chemotherapy and external beam radiation were widely adopted in North America and Europe, These trials included many investigational biases and were subjected to criticism concerning the improvement of 5-year survival rates [40].

Many trials evaluating the efficacy and toxicity of different drugs in metastatic or recurrent GC in the peritoneal cavity show controversial response rates but the median survival remains in the range of 6 to 16 months [41].

So the question which arises in this group is whether these patients may benefit from intraperitoneal chemotherapy after an aggressive surgical approach.

A meta-analysis reviewed all clinical IP trials in their different forms in resectable GC. The results demonstrated survival benefit in the IP arms but only one trial evaluating the role of HIPEC in gastric GC compared surgery+HIPEC vs. surgery alone [42].

Another very interesting approach in PC from GC is a novel multidisciplinary treatment combining bidirectional chemotherapy - neoadjuvant intraperitoneal (IP) plus systemic chemotherapy (NIPS) plus CRS and HIPEC and early postoperative IP chemotherapy (EPIC). The aim of NIPS is downstaging PC and increasing the incidence of complete cytoreduction [43].

A complete response after NIPS was obtained in 50% of patients with PC.

A phase III randomized trial in patients with GC and gastric PC demonstrated that CRS+HIPEC vs. CRS alone improved significantly the median survival (11 vs. 6.5 months; $p<0.04$).

Based on this data, a multicenter prospective randomized clinical trial started in 2007 by the EUNE (European Union Network of Excellence on Gastric Cancer).

This trial aims at studying the value of HIPEC to the current paradigm set by the MAGIC trials. Patients with serosal invasion (T_3-T_4), lymph node metastasis or patients with positive peritoneal cytology are included. All patients receive 3 cycles of systemic chemotherapy, followed by D_2 resection and then they are randomized either to undergo surgery+HIPEC or surgery alone [9]. All these results demonstrate that there is evidence for a slow progress in predicting fatal GC peritoneal recurrence [45].

A shift toward modern high-throughput screening technology over cancer genome structure in order to discover more reliable biomarkers, such as miRNAs, may help predict more accurately patients in high risk for PC development.

Colorectal cancer

Peritoneal disease continues to be a common mode of colorectal cancer progression since 8% of patients have synchronous peritoneal seeding at the time of initial operation, and 25% of patients with recurrence have their disease relapse confined within the peritoneal cavity [46].

The conventional treatment of PC from colorectal cancer is systemic multi-drug chemotherapy which has not altered the overall survival (median survival of 6-9 months) [47,48].

Since the development of new systemic chemotherapy protocols using irinotecan and oxaliplatin and of new targeting agents, such as monoclonal antibodies, the prognosis of metastatic colorectal cancer has improved with a median survival reaching 24 months.

The recent study of Sanoff and colleagues [50] presented 5-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer. Median survival was 20.2 months with 5% 5-year survival. The main bias of this study was that only 7% of the patients had PC and the authors did not provide data on objective response and survival for the subset of patients with PC.

Metastatic disease sites in the reported patients included mostly liver and lung in which response was readily measurable by radiological studies. Published evidence of long-term survival with systemic chemotherapy in the treatment of PC from colorectal cancer is lacking. Two year ago Elias et al. [50] reported a median survival of 23.9 months in 48 patients with isolated and limited colorectal peritoneal carcinomatosis only, treated with surgery and modern systemic chemotherapy.

In sharp contrast, a number of recent studies including a phase III study, have described treatment with CRS and HIPEC. This phase III study from the Netherlands Cancer Institute randomly assigned patients to receive either standard treatment of conventional surgery plus systemic chemotherapy with 5FU+leucovorin vs. CRS+HIPEC with mitomycin C and then systemic chemotherapy. At a median follow up of 21.6 months the median survival was 12.6 months in the standard group

vs. 22.3 months in the HIPEC group ($p<0.03$) [51]. The criticism in this study was that included 5FU+ leucovorin only as systemic chemotherapy and not the recent systemic protocols with oxaliplatin or irinotecan plus targeting therapies.

Another published multicenter study with over 500 patients with PC of colorectal origin reported that those treated with combination of CRS and perioperative IP chemotherapy experienced median survival of 32 months and 5-year survival of 27% [52].

Long-term results of the randomized Dutch trial comparing CRS+HIPEC vs. CRS+systemic chemotherapy showed that the benefits of the HIPEC arm were maintained over time with an 8-year follow up and the probability of survival at 10 years was 37% [53,54].

The question which arises at this moment is why is there still a degree of skepticism and limited acceptance among oncologists for CRS+HIPEC despite the large body of international publications on this modality? The answers proposed by the opponents of the method are that the first surgical procedure depends on the skills and the level of experience of the surgeon, and second there are variations in IP chemotherapy regimens used among the institutions which may, to some degree, contribute to the differences in the results. These two points may contribute to the not clear standardization of the technique.

For this reason the American Society of Peritoneal Surface Malignancies (ASPSM) consensus standardized HIPEC delivery in patients with colorectal cancer peritoneal dissemination (Table 2) [55].

Based on this data a prospective randomized clinical trial was designed by the Peritoneal Surface Oncology Group (PSOG) and the United States Military Cancer Institute (USMCI). This trial started in 2009 and is accruing patients with PCI<20 and good performance status. Patients will be randomly assigned to either best available systemic chemotherapy or CS+HIPEC followed by systemic chemotherapy. Patients that will fail systemic therapy will be allowed to cross over to the surgical arm [9]. Hopefully, this study will define the role of CRS+HIPEC in the management of PC of colorectal origin.

Table 2. American Society of Peritoneal Surface Malignancies standardized HIPEC delivery in patients with colorectal cancer with peritoneal dissemination

HIPEC method: closed
Drug: Mitomycin C
Dosage: 40 mg
Timing of drug delivery: 30 mg at time zero, 10 mg at 60 min
Volume of perfusate: 3 liters
Inflow temperature: 42° C
Duration of perfusion: 90 min

Another important question is whether to use this multidisciplinary approach for high risk patients with colorectal cancer in order to avoid peritoneal dissemination. The management of patients with minimal carcinomatosis must be the goal. Second look surgery in patients at high risk (Table 3) for locoregional failure in colorectal cancer needs to be considered. In this group of high risk patients Elias et al. [56] perform second look operation after the initial operation and 6 cycles of systemic chemotherapy with FOLFOX or FOLFIRI plus Avastin. This second look operation performed 3 months after the end of systemic chemotherapy in clinically asymptomatic patients revealed PC in 55% of the cases, which were treated with CRS+HIPEC without postoperative mortality.

Recently, another study from Greece [57] evaluated the effect of adjuvant perioperative IP chemotherapy in the treatment of locally advanced colorectal cancer. In this preliminary study patients with R0 resection at high risk to develop PC received either HIPEC (HIPEC group=40 patients) or early postoperative IP chemotherapy (EPIC group=67 patients). The 3-year survival rate was 100 vs. 69% ($p<0.01$) in favor of HIPEC and the incidence of recurrence in the EPIC group was higher than in the HIPEC group (63 vs. 19%; $p<0.009$) [57].

In this direction another trial from the National Cancer Institute is open [58] in order to evaluate the role of CRS+HIPEC in minimally PC performing a second look surgery in high risk patients.

Ovarian cancer

Ovarian cancer (OC) is the 5th leading cause of death among females in the USA and the majority of cases are diagnosed at an advanced stage; despite platinum-based systemic chemotherapy, the prognosis remains poor due to a high rate of recurrence [59].

The therapy of OC is dependent on the stage at diagnosis. Normally the treatment of newly diagnosed OC includes CRS followed by systemic chemotherapy combining a platinum compound and taxanes [60-62]. For patients in whom primary surgery is not feasible, primary chemotherapy is given, followed by interval

Table 3. Patients at high risk to develop peritoneal carcinomatosis of colorectal origin

Findings during the initial operation
T_4 tumor
Tumor perforated in the peritoneal cavity
Ovarian metastases synchronous to the primary
Few resectable peritoneal seeding
Positive peritoneal washings

debulking or CRS after 3 cycles of systemic chemotherapy.

However, 60-70% of patients will suffer disease recurrence, and the 2 most frequent recurrence patterns are in locoregional lymph nodes or peritoneal spread.

The main problem according to the initial treatment is to well define the kind of operation.

Complete cytoreduction for PSM teams means residual disease < 2.5 mm and for gynecologic oncologists optimal debulking means residual disease <1 cm. There is a huge difference between the tumor volume remaining postoperatively.

The principal goal of CS is to remove all primary disease and all metastatic disease since the size of the remaining disease is related to survival [63].

IP chemotherapy, as frontline therapy, combined with systemic chemotherapy, is attractive and a recent phase III study (GOG172) has shown to be superior to systemic chemotherapy alone [64].

The same results were achieved with postoperative IP chemotherapy and systemic chemotherapy, especially in the group of patients who received IP cisplatin 100 mg/m^2 with 49 vs. 41 months overall survival in the IP+systemic group [65].

In a study conducted in 2001, patients (n=462) with stage III OC and optimally debulking surgery were randomized between IV paclitaxel+cisplatin vs. IV carboplatin and paclitaxel+IP cisplatin. A survival benefit of 27.9 months vs. 22.2 months ($p<0.01$) favoring the IP group was observed [66].

The question which is under investigation is whether there is any role of HIPEC as frontline treatment or as second line treatment in patients with PC from OC.

Up until now only in a small number of case-control trials has been reported, showing a small advantage in the HIPEC group in women with PC from OC [67-69].

Spiliotis et al. [62] in a small phase III prospective trial evaluated the role of CRS and HIREC plus systemic chemotherapy vs. CRS plus systemic chemotherapy in women with recurrent OC after initial debulking surgery and systemic chemotherapy.

The median survival was 19.5 vs. 11.2 months ($p<0.05$) and the 3-year survival was 50 vs. 18% in favor of the HIPEC group [62]. These results were confirmed by other investigators in small number of patients in the last 10 years [62-69]. A prospective multicenter study is currently conducted by the Netherlands Cancer Institute with 3 cycles of neoadjuvant systemic chemotherapy followed by interval surgery with or without HIPEC.

One more recent study by Geelen et al. reported an overall survival rate of 37 months and a median progression free survival of 13 months in 42 patients with recurrent OC treated with CRS and HIPEC [70].

During the last 5 years utilizing laparoscopically assisted HIPEC becomes an excellent idea [71]. Esquirel et al. [72] reported the preliminary results from 14 patients with limited ovarian carcinomatosis in whom they were able to perform CRS laparoscopically in 77% of them; they also performed HIPEC by the same route. The most attractive point is the idea to utilize laparoscopically assisted HIPEC as neoadjuvant procedure in patients with advanced peritoneal dissemination to achieve disease downstaging with HIPEC [71,73].

In conclusion, the role of HIPEC in the management of PC from OC remains unclear. A large double-blind randomized clinical trial designed to address the role of CRS and HIPEC in recurrent or in chemoresistant OC is warranted. On the other hand, in the future it is important to discover molecular diagnostic tools for screening and genome structure variations in order to predict those women which are at high risk to develop PC [74].

Peritoneal mesothelioma

Once regarded as a rare and uniformly lethal disease, diffuse malignant mesothelioma (DMPM) is attracting growing scientific interest [75]. Some available evidence reports a benefit for systemic chemotherapy; especially the combination of cisplatin and pemetrexed shows promise compared with the modest activity seen with single-agent pemetrexed or cisplatin.

Numerous phase III studies demonstrated long-term benefit with CRS+HIPEC for the treatment of peritoneal mesothelioma [48,76,77]. Yan et al. in a systemic review reported a median survival of 53 months with 3- and 5-year survival rates of 60 and 47% respectively.

According all these literature data there is evidence that the standard of care for peritoneal mesothelioma is CRS with HIPEC plus systemic chemotherapy in selected patients. Treatment should be given at an PSM center.

Conclusions - Future prospects

During the last 50 years surgeons have been trying to effectively and curatively manage the peritoneal dissemination of cancer many decades before perioperative IP chemotherapy was introduced.

Not a single article reporting the success of surgery alone in the management of carcinomatosis has ever been published. On the other hand in the last two decades in many centres around the world specializing in PSM, CRS with HIPEC is now the gold standard of care in well-selected patients, presenting excellent long-

term survival results which give a ray of hope in these patients [1].

The major goal of cancer surgery is, *first* to remove completely the primary tumor and achieve a R0 resection; *second* to maximize all the possible locoregional control like total mesorectal excision (TME) in rectal cancer or D_2 gastrectomy in GC; and *third* to use CRS+HIPEC in well-selected patients with gastrointestinal cancer. In the future, continued clinical research into CRS+HIPEC is mandatory, and management of patients with low PCI will result in the best outcome. Second look surgery in patients at high risk for locoregional failure and phase III prospective trials need to be considered.

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