Reference number to be mentioned by correspondence : AG/OM200857

Surgery and intracavitary chemotherapy for Peritoneal Carcinomatosis from Colorectal Origin

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Abstract

A subset of patients with colorectal cancer (CRC) develops synchronous or metachronous isolated peritoneal disease. The development of peritoneal carcinomatosis (PC) can be conceptualized as a series of well defined steps including cell shedding, adhesion to mesothelial cells and underlying matrix, and invasion of submesothelial tissue. Surgical cytoreduction combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) has evolved as the standard of care in patients with mucinous appendiceal tumors including the pseudomyxoma peritonei syndrome. Recently, this approach was extended to patients with peritoneal carcinomatosis (PC) from non appendiceal CRC. In this review, we discuss the biological rationale, clinical methods, and oncological outcomes associated with cytoreduction and intracavitary chemotherapy in CRC patients suffering from peritoneal disease spread. (Acta gastroenterol. belg., **2008**, 71, **000-000**).

Introduction

Since the original description by Spratt in 1980, surgery followed by hyperthermic intraperitoneal chemoperfusion has evolved as the standard of care in low grade appendiceal mucinous tumors including the pseudomyxoma peritonei syndrome (1,2). Recently, this approach was extended to patients with peritoneal carcinomatosis (PC) from non appendiceal colorectal cancer. In parallel, an increasing number of centers in Belgium and worldwide is offering this complex therapy in patients suffering from peritoneal surface malignancy. Here, we review the mechanisms of PC development in colorectal cancer patients and critically discuss the rationale and results of surgery and intracavitary chemotherapy.

Incidence and prognostic significance of peritoneal cancer spread in colorectal cancer

In colorectal cancer (CRC) patients, the occurrence of peritoneal carcinomatosis often coincides with systemic disease, or manifests itself as a preterminal condition. It has been estimated that approximately three percent of CRC patients will present with peritoneal spread in the absence of systemic disease (3). In Belgium, where the incidence of CRC in 2004 was approximately 7500 new cases, this would translate to about 230 patients per year who would benefit from locoregional therapy for PC.

Recent clinical studies suggest that a specific genotype underlies the development of isolated peritoneal cancer spread. Varghese and coworkers found that TIMP-2, IGF-1, and HIF-1 alpha were upregulated only in peritoneal metastases, but not in liver metastases (4). In addition, several molecular pathways relating to cytokine and inflammatory response, cell growth, cell adhesion, cell proliferation, TGF signaling, and mTOR were distinct between peritoneal and liver metastases. A similar approach was used by Kleivi *et al.*, who found gains of chromosome arm 5p and several candidate genes (including PTGER4, SKP2, and ZNF622) mapping to this region to be significantly more common in peritoneal metastases compared to primary tumours or liver metastases (5). We recently compared gene expression between CRC liver metastases and isolated peritoneal metastases, and found 179 genes to be differentially expressed, related to immune response, cellular differentiation, epithelial to mesenchymal transition (EMT), and cell growth (6). Pathway analysis showed that IL-6 and TGF signalling were upregulated in peritoneal metastases.

The prognostic outlook of patients with palliatively managed PC from colorectal malignancy is grim : the French multicenter EVOCAPE 1 study found a median survival of 5.2 months (7). Systemic chemotherapy improves survival in metastatic colorectal cancer, but the presence of PC has been shown to be an adverse determinant of response and prognosis in patients treated with fluorouracil or irinotecan based systemic chemotherapy (8-10). Contrary to those with visceral metastasis, patients with PC are at risk of develop debilitating symptoms such as obstruction and ascites formation, while the risk of perforation induced by the VEGF inhibitor bevacizumab may be more pronounced (11).

Pathophysiology

The development of peritoneal carcinomatosis can be conceptualized as consisting of several well defined steps (12) (Fig. 1).

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Submission date :
Revised version :
Acceptance date :

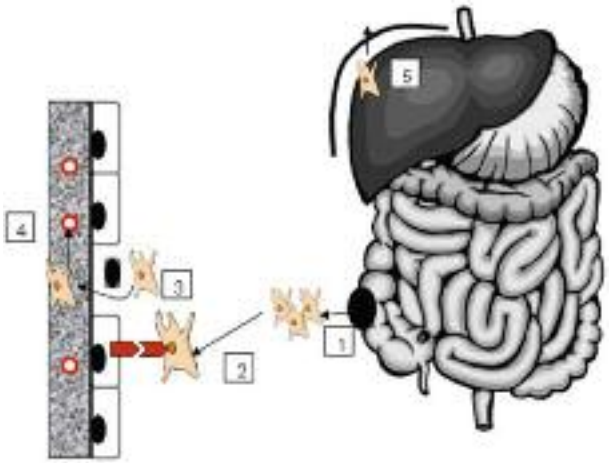

Fig. 1. — Illustration of the peritoneal metastatic cascade. Loose cancer cells are shed spontaneously or iatrogenically from the primary tumor (1). Tumor cells are then transported along predictable routes and adhere to the mesothelial layer by specific molecular interactions (2). Subsequently, cancer cells induce apoptosis of mesothelial cells (3) and gain access to the submesothelial stroma where vascular invasion may occur (4). Specialized structures in the diaphragm (stomata) facilitate systemic resorption of isolated cancer cells (5).

1. *Detachment of cells from the primary tumour*

The first step in the cascade resulting in PC is liberation of tumour cells from the primary cancer mass. This process can occur spontaneously, or can be iatrogenically caused. Also, downregulation of cell-cell adhesion molecules, such as E-cadherin via the transcription factor TWIST, has been reported to promote cancer cell detachment (13,14). Spontaneous shedding of loose cells is facilitated by the circumstance that the interstitial fluid pressure (IFP) in most solid tumours is abnormally high due to rapid cellular proliferation and lack of effective lymphatic drainage (15). Iatrogenic causes of peritoneal cancer spread include incomplete resection, inadvertent breach of the tumour's integrity, or section of blood or lymph vessels with subsequent leakage. This latter concept was proven by Hansen *et al.*, who detected tumour cells in the blood shed during oncologic surgery in 57 out of 61 patients undergoing cancer surgery (16). Importantly, the identified cancer cells demonstrated proliferation capacity, invasiveness, and tumorigenicity.

2. *Peritoneal transport*

Once liberated in the peritoneal cavity, loose cells are transported towards the pelvis and from the pelvis, along the right paracolic gutter, towards the subdiaphragmatic space (17). Moreover, cancer cells possess active motility provided by lamellipodia and filipodia, whose mechanical force is generated by polymerization of actin microfilaments, a process stimulated by membrane growth factor binding (18).

3. *Mesothelial adhesion*

The role of adhesion molecules in the pathogenesis of MRD has been reviewed recently (19). Adhesion of cancer cells to the mesothelial layer is mediated by the expression of VCAM-1, ICAM-1, and PECAM-1 (20,21). The expression of ICAM-1 is markedly enhanced by proinflammatory cytokines such as TNF-α (22). Other inflammatory mediators shown to increase mesothelial to cancer cell adhesion include IL-1β, IL-6, and the epidermal growth factor (23-25). As a consequence, intraperitoneal tumour growth has been shown to be related to the presence and extent of surgery induced peritoneal trauma (26,27). Alternatively, cancer cells may adhere to extracellular matrix (ECM) components. The omentum, characterized by immunocompetent cell aggregates ('milky spots') and a discontinuous mesothelial lining, represents a preferential location for peritoneal tumour implantation. The mechanisms responsible for this site specificity remain incompletely understood, but may relate to the pro-angiogenic environment elicited by the dense capillary network surrounding these immune aggregates (28).

4. *Invasion of the submesothelial layers*

Loose tumour cells gain access to submesothelial tissue at areas of peritoneal discontinuity. Alternatively, tumour cells were shown to induce apoptosis of mesothelial cells by a FAS dependent mechanism (29). Alternatively, the ECM might become exposed by contraction of mesothelial cells and disruption of intercellular junctions in response to inflammatory mediators (30). Invasion of the submesothelial tissue is accompanied by adhesion to and degradation of the existing ECM through various integrins and proteases respectively (31).

5. *Access to the systemic circulation*

Once the submesothelial stroma is invaded, cancer cells may gain access to the vascular and lymphatic microcirculation. Resorption of cancer cells into the systemic circulation may occur specifically through the diaphragm. The peritoneal lining of the diaphragm contains subperitoneal lymphatic lacunae located between muscle fibres of the diaphragm (32). These lacunae are reached through openings (stomata) between cuboidal mesothelial cells of the lacunar roof. From the subdiaphragmatic lymph channels, peritoneal fluid drains into substernal nodes and reaches the thoracic duct (33).

Selection and work-up of patients for surgical management

The decision to manage a patient with cytoreductive surgery and intraperitoneal chemotherapy should be made by a multidisciplinary team. Although the lack of large clinical trials hampers the formulation of solid selection criteria, a number of general selection

Table 1. — **Selection criteria for cytoreductive surgery in patients with peritoneal metastasis from colorectal origin**

Factors in favor of surgery
∞ Adequate performance status
∞ Completely resectable disease
∞ Absence of metastatic disease, with the possible exception of small and easily resectable liver metastasis
∞ Long disease free interval
Unfavourable circumstances
∞ Clinical presence of ascites
∞ Presence of subobstruction
∞ Progression under systemic chemotherapy
∞ Extensive involvement of the small bowel
∞ Disease present in all quadrants of the abdomen
∞ Signet cell differentiation

principles can be proposed based on the clinical experience of the last decades (Table 1) (34).

Small volume peritoneal surface malignancy is notoriously difficult to detect iconographically. Currently, ^{18}FDG-PET or PET-CT has emerged as the most accurate examination to detect recurrent colorectal cancer. Thus, a recent prospective study found ^{18}FDG-PET to have a sensitivity, specificity, positive predictive value, and negative predictive value of 96%, 92.1%, 89.2% and 97.2%, respectively in detecting colorectal cancer recurrence although in two patients the diagnosis of PC was missed (35). Diagnostic laparoscopy is generally discouraged because of the difficulty to adequately examine all peritoneal surfaces in often scarred abdomens, and because the real risk of subsequent surgical site metastasis.

Cytoreductive surgery for peritoneal carcinomatosis

Cytoreduction procedures are largely similar to any major abdominal surgery, but some technical aspects such as the performance of a peritonectomy are specific to the procedure. Technically, the upper abdomen (diaphragm, liver hilus, lesser omentum) is more difficult to render tumour free compared to the lower abdomen and pelvis. Since the complete procedure can take several hours, careful measures should be taken to prevent hypothermia and vascular or nerve injury caused by suboptimal patient positioning. Also, surgery should be swift but as bloodless as possible with liberal use of ultrasonic shears, argon coagulation, and vascular staplers.

Rationale for hyperthermic intraperitoneal chemoperfusion (HIPEC)

The main rationale for intraperitoneal (IP) drug delivery is the enhancement of the therapeutic index that can be obtained by exploiting the peritoneal barrier function. Indeed, this barrier function allows to administer a much higher cytotoxic drug dosage and this will result in increased efficacy by eradicating small (< 5 mm) residual tumour deposits and loose cancer cells (36). In the setting of stage III ovarian cancer, several large randomized trials have shown IP chemotherapy to be superior to standard intravenous chemotherapy in the primary chemotherapeutic management of small-volume residual disease (37). When used immediately following surgery, IP drug administration allows to treat the peritoneal cavity in its entirety, which is impossible to achieve once postoperative adhesions have developed. The ability of IP administered drug to penetrate tumour tissue depends on a number of variables related to the drug (molecular weight, mass, charge, solubility), the tumor (vascularity, interstitial pressure, matrix composition, density), and the mode of administration (dose, concentration, intraabdominal pressure, temperature).

Traditionally, intraperitoneal chemoperfusion is administered under hyperthermic conditions (temperature > 40° Celsius). A detailed discussion of the molecular and cytological effects of hyperthermia is beyond the scope of this paper. Interested readers are referred to an excellent recently published review (38). Briefly, the rationale for the addition of hyperthermia is based on 1. the selective antitumoural effects of hyperthermia ; 2. synergism with both radiation and chemotherapeutic drugs ; and 3. modulation or reversal of drug resistance. Preclinical studies have shown that the efficacy of mild hyperthermia (40°-41°C) is at least similar to that of more pronounced hyperthermia (39,40).

Technically, chemoperfusion is performed as a closed circuit consisting of a roller pump, heat exchange element, and one or more inflow and outflow drains. Depending on the type of cytotoxic drug, the duration of the chemoperfusion is between 30 and 90 minutes.

Choice of chemotherapy for intraperitoneal chemoperfusion in colorectal cancer

A rational choice of cytotoxic drug for IP delivery should be based on its activity profile, cell cycle specificity, locoregional toxicity profile, and, to a lesser extent, on demonstrated thermal enhancement (Table 2). In colorectal cancer, oxaliplatin (usually 460 mg/m^2) in monotherapy is currently the best studied drug for IP delivery. Because the agent has to be administered in a dextrose 5% solution, important hyperglycemia and electrolyte shifts during the chemoperfusion should be anticipated (41,42).

Toxicity and complications of cytoreduction and HIPEC procedures

Although cytoreduction with HIPEC represents a considerable undertaking, the associated mortality and morbidity do not differ from that of other major abdominal procedures. Published mortality ranges from 3-8% while postoperative morbidity rates from 20%-50% have been described (43,44). Because of the peritoneal barrier

Table 2. — **Pharmacokinetic and pharmacodynamic properties of cytotoxic agents used during intraoperative or early postoperative intraperitoneal chemotherapy**

Drug	MW (Da)	Ip dose (mg/m^2)	AUC ratio*	Drug penetration distance	TE
Alkylating agents					
Mitomycin C	334.3	35	10-23.5	2 mm	+
Platinum compounds					
Cisplatin	300.1	90-120	13-21	1-3 mm	+
Carboplatin	371.3	350-800	1.9-5.3	0.5 mm	+
Oxaliplatin	397.3	460	3.5	1-2 mm	+
Antimicrotubule agents					
Paclitaxel	853.9	20-175	NA	> 80 cell layers	?
Docetaxel	861.9	40-156	207	NA	+
Topoisomerase Interactive Agents					
Topotecan	457.9		NA	NA	?
Irinotecan	677.2		NA	NA	±
Mitoxantrone	517.4	28	15.2	5-6 cell layers	±
Doxorubicin	543.5	60-75	162	4-6 cell layers	+
Antimetabolites					
5-Fluorouracil	130.1	650	NA	0.2 mm	–

MW, molecular weight ; ip, intraperitoneal ; TE, thermal enhancement ; NA, not available ; AUC, area under the concentration-time curve ; *only data referring to clinical studies with hyperthermic chemoperfusion.

function, the drug plasma concentrations during and immediately after the chemoperfusion remain low and systemic toxicity is therefore rarely observed. The toxicity of hyperthermia consists mainly of prolonged postoperative ileus and temperature dependent edema of the small bowel. In animal models, colonic anastomotic healing was impaired by a combination of hyperthermia with either chemotherapy or radiotherapy, but not by hyperthermia alone (45-47). Jacquet *et al.* noted increased morbidity and mortality with rising intra-abdominal target temperature (48). Therefore, and taking into account its equivalent antitumoural efficacy, mild hyperthermia is by far the safest option.

Clinical results of cytoreduction and HIPEC in patients with colorectal cancer

A recent systematic review showed that the median overall survival following cytoreduction and HIPEC ranges from 13 to 29 months, and 5-year survival rates from 11% to 19% (49). When complete cytoreduction can be achieved, however, a median overall survival from 28 to 60 months and 5-year ranging from 22% to 49% can be expected. Since complete surgical resection has repeatedly been shown to represent the most important prognostic factor, randomized trials comparing systemic chemotherapy alone versus cytoreduction and HIPEC may not be feasible or ethical. This situation is similar to the setting of resectable colorectal liver metastases, where resection is considered the standard of care despite the absence of randomized comparisons of surgery versus systemic chemotherapy. Nevertheless, one small randomized trial has been reported comparing palliative systemic chemotherapy (fluorouracil) with cytoreduction and HIPEC in colorectal cancer patients (50). The results showed a significantly better median overall survival in the surgery and HIPEC group (22.3 months versus 12.6 months ; $P = 0.032$). The recently reported long term results of this trial showed a 5 year survival of 45% in patients who underwent a macroscopically complete resection (51). It should be noted that this trial was initiated before the availability of modern more active palliative chemotherapy regimens. Similar results were described in a recent multicenter retrospective series of 506 patients who underwent cytoreduction and HIPEC (52). Overall, median survival was 19.2 months ; results were significantly better when a complete cytoreduction could be achieved (32.4 months versus 8.4 months, $P < 0.001$). Lymph node and liver involvement, neoadjuvant chemotherapy, and poor histological grade adversely affected survival.

Conclusions and future prospects

Over the last decades, multimodality therapy encompassing surgery and HIPEC has been proven to provide a significant survival benefit in selected patients with PC. In experienced hands, treatment related toxicity is comparable to that of any major abdominal surgery. Patients in whom a complete resection is feasible reap a maximal benefit and may survive many years.

Several questions remain, however, unanswered. First, it is unclear whether the addition of HIPEC to cytoreduction adds to the efficacy of the procedure. At least two randomized trials comparing cytoreduction anlone versus cytoreduction and HIPEC are addressing this question (NCT00769405, Federation Nationale des Centres de Lutte Contre le Cancer, France and NCT00454519, Wuhan University, China). Second, more prospective clinical trials are needed to define

optimal selection criteria and to standardize treatment variables such as type of chemotherapy, dosage, duration, and target temperature. Also, the role of neoadjuvant and adjuvant systemic chemotherapy is at present undefined. Finally, basic and translational research is needed to gain a more profound insight into the molecular and genetic mechanisms underlying the peritoneal metastatic cascade.

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