Review article

Intraperitoneal chemotherapy for prevention and treatment of peritoneal carcinomatosis from colorectal origin

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SUMMARY

The peritoneal surface remains an important failure site for patients with colorectal cancer. Peritoneal metastases of colorectal cancer are at present considered equal to distant metastatic disease. Consequently, peritoneal carcinomatosis is treated with systemic chemotherapy and surgery only to palliate complications such as obstruction. Despite the development of new chemotherapeutic agents and combinations, the results remain disappointing with a limited impact on survival. Colorectal carcinoma cells are relatively resistant to chemotherapy. Intraperitoneal chemotherapy seems to be an attractive approach in the treatment of high-risk colorectal cancer and peritoneal carcinomatosis of colorectal origin providing high local drug concentration with limited systemic side effects. Adjuvant early postoperative intraperitoneal chemotherapy is worthwhile considering as a treatment option after resection of high-risk colorectal cancer. Meta-analysis of randomized trials demonstrates a positive impact of this adjuvant treatment on overall survival and regional tumor control. In the treatment of peritoneal carcinomatosis postoperative intraperitoneal chemotherapy leads to inadequate exposure of the peritoneal surface. Only intraoperative continuous peritoneal perfusion chemotherapy performed with direct cytotoxic drugs such as MMC and cisplatin may overcome this problem. The limited drug penetration in tissue implies the need for extensive cytoreductive surgery. Additionally, the latter form of regional chemotherapy can be performed under hyperthermic conditions. Hyperthermia has a direct cytotoxic effect and enhances the activity and penetration depth of many cytotoxic drugs. The results of phase II studies of cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin suggest that an increased median survival can be achieved with this approach, especially in patients with no macroscopic or small volume residual disease.

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INTRODUCTION

Incidence

Despite advances in adjuvant therapy, the peritoneal surface still remains an important failure site for patients with colorectal cancer. The incidence of peritoneal carcinomatosis as site of treatment failure is not accurately known, as the routine clinical follow-up examinations used by most investigators are likely to miss the diagnosis in the early stage. In various series, initial failure at the peritoneal surface is reported in 10-20% of patients after curative colon cancer resection, while the peritoneal surface is involved in 40-70% of such patients who present with recurrent disease. In less than 5-8% of all colon cancer patients and in 10-35% of all patients with recurrent disease, tumor recurrence is confined to the peritoneal surface only.[1-5] The most accurate assessment is obtained by thorough exploration of the abdominal cavity by the surgeon to determine the status of the complete peritoneal surface. At second laparotomy performed for mainly symptomatic, but also unrelated reasons, peritoneal seeding has been observed in approximately half of the patients, while it was the only site of recurrence in 2-18%.[3-6] Peritoneal seeding may also be

observed at diagnosis or surgical treatment of the primary tumor. At initial diagnosis of colon cancer, the peritoneal surface is involved in approximately 10-15% of all patients.[3-5] In patients with disseminated colon cancer at presentation, the peritoneal surface is involved at laparotomy in 30-50% of cases.[3-5]

Etiology

The high incidence of tumor implantation on the peritoneal surface in the management of colorectal cancer might be due to free intraperitoneal tumor emboli as a result of serosal penetration by the tumor.[7,8] Local serosal involvement of the tumor is a consistent predictor of subsequent intraperitoneal recurrence.[9] Even in stage I disease, in one out of four patients isolated tumor cells are detectable within the peritoneal cavity before manipulating the tumor.[10] In 15% of the resected specimen, free colorectal cancer cells can be determined on the peritoneal or perirectal surface of the bowel.[11] Other causes might be leakage of malignant cells into the peritoneal cavity from transected lymphatic channels or by venous blood backflow from the tumor site as well as direct dissemination from the cancer specimen as a result of surgical trauma. Fibrin entrapment of intra-abdominal cancer cells on traumatized peritoneal surfaces and progression of the entrapped cells through growth factors involved in the wound healing process may also play an important role in the development of peritoneal carcinomatosis.[7,8]

Natural history and survival with systemic chemotherapy

The natural history of peritoneal carcinomatosis from colorectal origin is associated with a mean and median survival of only 6-7 and 5-9 months respectively.[12,13] Survival of untreated patients varies from less than one month to almost 5 years.[13] Peritoneal metastases of colorectal cancer are at present considered equal to distant metastatic disease. Consequently, peritoneal carcinomatosis is treated with systemic chemotherapy and surgery only to palliate complications such as obstruction. The combination of 5-fluorouracil (5-FU) and leucovorin is most commonly used. Despite the development of new chemotherapeutic agents and combinations, the results remain disappointing, with response rates of approximately 25% and a limited impact on survival.[14-17] 1 and 2-year survival rates after palliative surgery and systemic chemotherapy for metastatic colorectal cancer are reported to be 35-50% and 10-20% respectively.[18-22] Colorectal carcinoma cells are relatively resistant to chemotherapy. Higher dosages seem to be associated with increased response rates.[17,18] However, more effective intravenously administered dose levels of 5-FU are associated with intolerable systemic side effects.[7]

Regional treatment

Recently, Sugarbaker has emphasized that peritoneal carcinomatosis can better be understood as regional spread.[7,23-25] Tumor implants on peritoneal surfaces may remain confined to the peritoneal cavity for prolonged periods of time. This means that it is certainly a poor prognostic sign, but not a proof of distant metastases, and provides a rationale for regional therapy.[26] The feasibility and efficacy of different kinds of regional treatment for peritoneal carcinomatosis of colorectal origin have been investigated. Some of them are still very experimental and only investigated in animal models. Other treatment modalities are now the subject of phase III studies. So far, results of clinical studies on intraperitoneal immunotherapy,[27,28] radioimmunotherapy[27,28] and photodynamic therapy [29-33] have not demonstrated significant therapeutic benefit, when compared with systemic chemotherapy. In this paper we will discuss the available data on intraperitoneal chemotherapy in the management of colorectal cancer.

THE RATIONALE FOR INTRAPERITONEAL CHEMOTHERAPY

Regional chemotherapeutic treatment modalities are nowadays widely used for sarcoma and melanoma of the limbs, secondary liver neoplasms and locally advanced intra-abdominal tumors, using isolated perfusion or intra-arterial infusion of the extremity, organ or abdominal area. During the last decades, intraperitoneal chemotherapy as treatment modality of primary and secondary peritoneal malignancy has been investigated. Recently, we have published on the issue of the rationale for more extensive use of intraperitoneal chemotherapy.[34] It will be discussed briefly in this paper.

Pharmacological basis

The major advantage of intraperitoneal chemotherapy is the regional dose intensity provided. Following intracavitary drug administration, the peritoneal surface is exposed to higher concentrations than the rest of the body, resulting in less systemic toxicity when compared to conventional intravenous drug administration.[24,35] Assuming a dose-effect relation, a higher efficacy of the cytotoxic drug may be achieved in this way. The concentration differential arises because of the relatively slow rate of movement of the drug from the peritoneal cavity into

the plasma (peritoneal clearance). This pharmacokinetic process is based on the characteristics of the peritoneal-plasma barrier, which maintains the continuous high ratio of chemotherapeutic drug concentration between peritoneal cavity and plasma.[36] The physical nature of the peritoneal-plasma barrier has not been clearly defined. At present, it is suspected that a diffusion barrier exists that consists of subserosal tissue or blood vessel walls. The capillary wall appears to offer the dominant resistance to the transfer of large molecules. The mesothelium and peritoneal interstitium impede their movement to a lesser extent. The extensive removal of peritoneum during cytoreductive surgery does not seem to affect the pharmacokinetcs of early postoperative intraperitoneal chemotherapy.[37] Depending on their molecular weight, their affinity to lipids, and first-passage effect and clearance by the liver, the drug exposure to the peritoneal cavity may be up to 1400 times higher than in the systemic exposure, measured in the peripheral blood (table 1).[23,35-44] An additional advantage is that the blood drainage of the peritoneal surface through the portal vein to the liver provides an increased exposure of potential hepatic micrometastases to intraperitoneally administered cytotoxic drugs. High intraportal 5-FU concentrations may be achieved, i.e. 3-4 times the systemic concentrations. 5-FU delivery to the liver after intraperitoneal administration equals the amount of drug entering the liver during intrahepatic artery infusion.[45]

When 5-FU incorporated in microspheres was delivered intraperitoneally in mice with peritoneal colon carcinoma, a slow release of 5-FU over 3 weeks was established. This resulted in an increased drug exposure to the intraperitoneal tissues with lower blood plasma concentrations.[46]

Table 1. Mean or median peritoneal cavity/plasma area under concentration versus time curve (AUC) ratio after intraperitoneal infusion of some agents active against colon cancer.[23,34-44]

Agent	Mean or median peritoneal cavity/plasma AUC ratio
Cisplatin	12 – 20
Carboplatin	18
Melphalan	65
Mitomycin-C	75 – 80
5-Fluorouracil	250 – 1400
5-Fluoro-2'-deoxyuridine	430 - >1000
Leucovorin	35 – 45
Mitoxantrone	1400
Topotecan	54
Tumor necrosis factor μ	4854
Irinotecan (SN-38*) #	14 (4)
Oxaliplatin #	6 – 17
MTA #	19 – 41

μ = only determined during HIPEC,

* = active metabolite of irinotecan,

= only determined in rodents,

MTA = multi-targeted antifolate

Preconditions and patient selection

Some prerequisites for useful intraperitoneal chemotherapy can be defined (table 2). Patients with additional hematogenic metastases should obviously not be treated by this approach.[24] Homogeneous distribution and drug exposure to the entire seroperitoneal surface is required. This implies the need for lysis of intra-abdominal adhesions and the use of large volumes of fluid containing the chemotherapeutic agent. The disadvantage of intracavitary chemotherapy is the limited tissue penetration by the therapeutic agent, estimated to be maximal 3 to 5 mm.[47-51] This implies the need for extensive cytoreductive surgery to precede intraperitoneal delivery of drugs in the treatment of peritoneal malignancy. The objective of optimal cytoreductive surgery is to leave no macroscopic tumor behind or, when this can not been achieved, only tumor deposits of less than 2.5 mm in size. If a deposit is infiltrating deeply into an organ and it is impossible to peel the malignancy from its surface, the involved organ, or a segment of it, has to be resected. When parietal peritoneal surfaces are significantly involved, peritonectomy procedures, as described by Sugarbaker[52], should be performed.

The biological aggressiveness of a peritoneal surface malignancy will have profound influence on treatment results. Non-invasive tumors may have extensive spread on peritoneal surfaces and yet be completely resectable by peritonectomy procedures. Also, these non-invasive malignancies are extremely unlikely to metastasize to lymph nodes or to systemic sites. Therefore, these patients, in particular, are likely to benefit from this intraperitoneal chemotherapy approach. Pseudomyxoma peritonei is the prime example of this situation. However,

Table 2. Preconditions for intraperitoneal chemotherapy.

- Absence of hematogenous metastases
- Optimal surgical cytoreduction/Minimal residual disease
- Homogeneous distribution (lack of adhesions, intestinal mobilization, large fluid volume)

the histological classification of pseudomyxoma peritonei is not uniform. A gradual scale from benign pseudomyxoma peritonei to more invasive appendiceal mucinous adenocarcinoma exists.[53,54] Different pathologists may classify the same specimen as benign pseudomyxoma peritonei or as low-grade mucinous adenocarcinoma of the appendix. If only the clearly benign form is classified as pseudomyxoma, higher survival rates might be expected in both the pseudomyxoma peritonei patients, but also in patients with well differentiated mucinous appendiceal carcinoma. Comparison of results from different studies is therefore difficult as long as no generally accepted histological criteria are applied.

Other considerations

During peroperative and immediate postoperative intraperitoneal chemotherapy the abdominal cavity is filled with a large volume of fluid that may decrease fibrin accumulation and eliminate tumor cells from the abdomen before they fix with scar tissue. The achieved elimination of platelets, white blood cells and monocytes from the abdominal cavity may also diminish the production of tumor growth associated with the wound healing process.[23] Potential disadvantages of this treatment strategy include the morbidity associated with extensive cytoreductive surgery, increased local toxicity and the lack of optimal treatment of occult systemic metastases. Because of the latter, after intraperitoneal chemotherapy patients will also receive adjuvant systemic chemotherapeutic treatment in some centres.

INSTILLATION INTRAPERITONEAL CHEMOTHERAPY

History

Intraperitoneal chemotherapy began with the simple instillation of the drug in the peritoneal cavity. In 1955, Weisberger et al.[55] reported the results in intraperitoneal nitrogen mustard treatment of seven patients with ovarian cancer. Impressive control of malignant ascites was observed. However, this and other early clinical studies of intraperitoneal drug administration were unable to demonstrate any impact on intra-abdominal tumor masses, and the toxicity of the procedure was substantial, principally abdominal pain. Therefore, this therapeutic approach was abandoned until the 1980s, when several phase II trials studied the efficacy of intraperitoneal installation of cisplatin in ovarian cancer patients.[34,56]

Timing

Intraperitoneal chemotherapy has been administered in the preoperative, intraoperative, and early and late postoperative period.[57] From a distribution point of view, the optimal time for intraperitoneal chemotherapy administration is prior to any surgery or during the intraoperative period. Requirements for preoperative administration, which has as objective to facilitate subsequent cytoreductive surgery, are small-volume disease and lack of extensive adhesions from previous operations. Intraoperative and early postoperative intraperitoneal therapy are intended to consolidate the effect of surgery by causing lethal damage to residual small tumor noduli and microscopic intraperitoneal malignant cell localizations. Uniform exposure of all surfaces within the peritoneal cavity is of critical importance to achieve this goal. Infusion of large volumes (1-2 liters) of fluid is necessary to achieve this goal.[11,58,59] The mechanism of drug action has a direct impact on the scheduling of intraperitoneal chemotherapy. 5-FU, an anti-metabolite, is only effective with prolonged administration, making short intraoperative administration inappropriate. 5-FU has been used for continuous intraperitoneal treatment during the first 5 postoperative days. Non-cell-cycle, direct cytotoxic, agents such as cisplatin and MMC, whose effect is enhanced under hyperthermic conditions, require only a short time to produce a cytoxic effect and are usually selected for intraopertive (hyperthermic) intraperitoneal chemotherapy. Hyperthermic intraperitoneal chemotherapy is not tolerable to an awake patient, making its application only possible intraoperatively. Late postoperative intraperitoneal chemotherapy, later than 2 weeks after surgery, is associated with loss of therapeutic effect, probably due to lack of uniform distribution, mainly caused by postoperative adhesions, and catheter related problems.[57]

Peritoneal access devices

Access to the peritoneal cavity for instillation of chemotherapeutic solutions is usually achieved by placement of a Tenckhoff catheter or a subcutaneous implantable port and catheter (Port-A-Cath) system. Despite the development of other types of catheters especially designed to minimize catheter-related complications, the average incidence of complications has not been diminished over the past decades.[60-63] Complications of the peritoneal access device include failure to place the catheter successfully, bowel perforation during placement (1-4%), obstruction of inflow (1-4%), failure of outflow (23-45%), pain during infusion, subcutaneous leakage (1-11%), infectious complications, as well local infection such as peritonitis (6%), and, rarely, hematoma or bleeding.[60-62]

Treatment schedules

5-FU is most often used for instillation intraperitoneal chemotherapy for colorectal cancer and is sometimes combined with intravenous chemotherapy. Usually, the intraperitoneal chemotherapy treatment consists of administration of the drug diluted in 1.5-2 liters of isotonic or dialysis fluid into the peritoneal cavity in approximately one hour, where it is left until the next day. In experimental models, the use of a hypertonic carrier solution prolonged the exposure to the drug and increased the drug availability at the peritoneal surface.[64] Frequent changes in the patient's position are encouraged to ensure distribution of the drug. The next day the fluid is drained in approximately one hour. This might be repeated for 4 to 5 consecutive days every month over a 6-12 month period.[24,65,66] Others give early postoperative intraperitoneal chemotherapy as adjuvant treatment for high-risk colon cancer only for 6 consecutive days.[58,67]

Chemotherapy related morbidity

Early postoperative instillation intraperitoneal chemotherapy has been used in patients with colorectal malignancies less than in cases of ovarian cancer.[65-72] The total number of immediate and delayed serious complications after intraperitoneal administration of 5-FU in colorectal patients is comparable to that after intravenous administration, although the nature of these complications differs markedly between the two routes of drug administration.[58,66-70] The major toxicities of intraperitoneal infusion of 5-FU and MMC in these patients are abdominal pain and bone marrow depression.[58,66-71] Although in experimental models, healing of intestinal anastomotic suture lines is impaired when exposed to early postoperative intraperitoneal chemotherapy,[73-76] clinical randomized studies have failed to demonstrate this.[58,65-67] Severe intra-abdominal fibrosis may occur after intraperitoneal administration of 5-fluoro-2'-deoxyuridine (floxuridine, FUDR), an active metabolite of 5-FU which is often used in hepatic artery infusion for liver metastases, and leucovorin. It might present as an intra-abdominal mass mimicking even colon cancer recurrence.[77] Instillation intraperitoneal chemotherapy is not fully completed because of complications in approximately 25-35% of cases.[58,66,67]

Results of clinical studies

Three phase III studies on early postoperative intraperitoneal chemotherapy as an adjuvant treatment in patients with resectable colorectal cancer and at high risk of developing recurrent disease have been conducted (table 3).[65-67] Meta-analysis of the three randomized studies, using the chi-squared test, revealed a highly significant difference in survival in favour of patients treated by adjuvant intraperitoneal chemotherapy.[78] The 5-year overall survival rates were 62% versus 41% ($p<0.001$). However, regarding the 5-year disease free survival, no statistically significant difference, but only a trend in favour of intraperitoneal chemotherapy was observed (59% versus 52%, $p=0.077$). The peritoneal failure rate was significantly lower for the intraperitoneal chemotherapy

Table 3. Results of phase III studies on adjuvant early postoperative intraperitoneal chemotherapy for high-risk colon cancer.

Authors	Adjuvant treatment	n	5-year survival*	5-year DFS	peritoneal failure
Sugarbaker et al.[66]#	i.p. 5-FU	36	43% *	52% *	2/10 a
	i.v. 5-FU	30	46%	57%	10/11
Scheithauer et al.[65]	i.p.+ i.v. 5-FU/LV	117	85% §	78% ¶	2% b
	i.v. 5-FU + levamisole	119	66%	61%	5%
Vaillant et al.[67]	perop. I.v. + i.p. 5-FU	133	74% *	68% *	7.5% g
stage II and III	no adjuvant treatment	134	69%	62%	9.7%
Vaillant et al.[67]	perop. I.v. + i.p. 5-FU	20		89% +	
stage II only	no adjuvant treatment	20		73%	
Meta-analysis of the	i.p. (+/- i.v.)	286	62%c	59%x	5%µ
three series[78]	control arm	283	41%	52%	11%

n = number of patients, * = overall survival, DFS = disease free survival, # colon and rectal cancer patients, in the other studies only colon cancer patients, 5-FU = 5-fluorouracil, * non-significant difference, § $p = 0.0004$, ¶ $p = 0.0015$, + $p = 0.05$, a peritoneal recurrence rate at relaparotomy, $p = 0.03$, b peritoneum at first and only site of histological proven recurrence, p-value not mentioned, g = peritoneal recurrence detected at clinical and radiological examination, p-value not mentioned, c $p<0.001$, x $p=0.077$, µ $p=0.025$.

group than the control group (5% versus 11%, p=0.025). It has to be noted that both intraperitoneal treatment and treatment of patients in the control group differed widely among all three studies, and the method of detection and the definition of peritoneal recurrence were also hardly comparable. In an interesting pilot study, Kelsen et al.[42] examined immediate postoperative intraperitoneal adjuvant chemotherapy using the agents FUDR and leucovorin followed by systemic treatment with 5-FU and levamisole in a group of 26 patients. This regimen was reasonably well tolerated and after a median follow-up of 18 months, there were only four recurrences observed, which were localized outside the peritoneal cavity.

Unfortunately, no randomized phase III studies have been conducted to investigate this modality as *treatment of peritoneal carcinomatosis* of colorectal origin. Most reported studies concern small series with mixed primary cancer.[71,79] A few larger series have been published (table 4).[69,72,80,81] Sugarbaker et al.[69] reported on the excellent results of treatment of 130 appendiceal carcinomas with peritoneal spread. These results are, however, obtained in a group of patients with a mainly low-grade appendiceal carcinoma, of which many cases could probably be diagnosed as pseudomyxoma peritonei by others (see discussion above). Therefore, these results might be less impressive for cases of true appendiceal carcinoma. In the series of Sugarbaker, survival rates varying from 20% to 99% in various subgroups of colorectal and appendiceal cancer patients were observed. Limited spread over abdominopelvic regions, small tumor noduli, absence of lymph node metastases, low grade and intestinal histological type and optimal cytoreduction, leaving tumor residue smaller than 2.5 mm behind, were favourable prognostic factors.[69,81] Culliford et al.[72] reported 28% 5-year survivors in a mixed group of 64 patients with peritoneal metastases from colorectal and appendiceal origin, including also pseudomyxoma peritonei patients, treated with early intraperitoneal chemotherapy with FUDR and leucovorin.

Sugarbaker [82] also reported on the effectiveness of *induction intraperitoneal chemotherapy* with 5-FU, combined with intravenous MMC, in 26 patients with peritoneal carcinomatosis from colon or appendiceal cancer. Complete and partial responses were observed during laparotomy only in patients with low- and moderate-volume disease, facilitating the surgical procedure. This positive effect was, however, associated with an increased surgical complication rate, compared to matched patients without this induction chemotherapy prior to cytoreductive surgery.

Intraperitoneal administration of topotecan, a new agent active against recurrent colon cancer, has been so far only studied in patients with recurrent ovarian cancer.[44] Other new and modified agents have been investigated for their therapeutic effects in experimental models (table 1). Intraperitoneal administration of 5-FU incorporated in microspheres and irinotecan (CPT-11) in rodents resulted in decreased toxicity and significantly increased effectiveness in control of peritoneal seeding compared to intraperitoneal conventional 5-FU and intravenous CPT-11 administration.[38,41,42]

In conclusion, these studies demonstrate that some locoregional therapeutic benefit may be expected from intraperitoneal chemotherapy and that it might be advisable to combine this treatment with systemic chemotherapy to also reduce the risk of distant metastases. However, early postoperative intraperitoneal chemotherapy, with the simple infusion of the drug into the peritoneal cavity through a peroperatively placed catheter, seems to be associated with inadequate distribution of the drug to the entire seroperitoneal surface and was considered to be responsible for the high recurrence

Table 4. Results of larger studies on cytoreductive surgery and early postoperative intraperitoneal chemotherapy for peritoneal dissemination of colorectal and appendiceal cancer.

First author	Year	n	Site	FU in months	1-, 2- & 3-year overall survival			Remarks
Sugarbaker[65]	1995	130	A	24*	90%,	70%,	65%	mainly low-grade, + systemic chemotherapy
Sugarbaker[77]	1996	64	CR	12	60%,	35%,	25%	+ systemic chemotherapy
Elias[76]	1997	23	CR	12**	85%,	55%,	40%	1-year DFS 53%, peritoneal recurrence 25%
Culliford[132]	2001	64†	CRA	17	85%,	60%,	35%	5-year overall survival 28%

n = number of patients, † = including 6 patients with pseudomyxoma peritonei, C = colon, R = rectum, A = appendix, FU = mean or median follow-up period, * = median follow-up for all 130 appendiceal cancer patients and 51 colorectal cancer patients, ** median follow-up for all 54 patients with peritoneal carcinomatosis of different origin, DFS = disease-free survival.

rate.[57,83] This resulted in the application of peroperative intraperitoneal perfusion chemotherapy.

INTRAOPERATIVE HYPERTHERMIC INTRAPERITONEAL PERFUSION CHEMOTHERAPY

Intraoperative intraperitoneal perfusion chemotherapy results in a more uniform distribution of the cytotoxic drug throughout the abdominal cavity. Additionally, it can be performed under hyperthermic conditions. Hyperthermia has a direct cytotoxic effect at a level exceeding 42 °C and enhances the activity and the penetration depth of many cytotoxic drugs already above 39 °C.[51,84-86] Cytoreductive surgery with continuous hyperthermic perfusion peritoneal chemotherapy (CHPPC) is a relative new regional combination treatment of primary and secondary peritoneal malignancy. The first clinical report on this treatment modality was published in 1980. Spratt et al.[87] had performed this treatment successfully on a patient with pseudomyxoma peritonei. Especially during the last decade, more attention has been paid to this treatment modality and more clinical experience has been gained. Application of this approach in patients with pseudomyxoma peritonei, malignant peritoneal mesothelioma and peritoneal dissemination of gastric carcinoma have demonstrated promising results regarding survival benefit.[53,88-98] In cases of gastric carcinoma with serosal invasion in the absence of peritoneal dissemination CHPPC has been performed successfully as an adjuvant treatment to primary resection.[99-104] This technique is nowadays used in more than 30 centres worldwide.[105] However, the experience of this regional cancer treatment in peritoneal seeding from colorectal origin is still relatively limited.[106-121]

Different techniques

The CHPPC-procedure has not yet been standardized regarding indication, duration of the perfusion, intra-abdominal temperature during hyperthermia, open or closed perfusion models and kind and dosage of chemotherapeutic agents used. To optimize exposure of the surface of the abdominal organs and the parietal peritoneum to the perfusate peritoneal expansion is applied in some centres. This may be achieved by different methods.[53,90,91,110,122,123] There are as yet no data available to demonstrate one of the methods to be more effective. Additionally, a recent animal study demonstrated that the raised intra-abdominal pressure, which accompanies peritoneal cavity expansion in a closed-abdomen model, might increase drug penetration into tissue.[124] On the other hand, a closed-abdomen model might be associated with inhomogeneous drug and heat distribution.[121,123]

Chemotherapeutic agents

Considerations for the choice of the chemotherapeutic drug are summarized in table 5. 5-FU is not suitable for this application, because the exposure duration is too short for this anti-metabolite to be effective In CHPPC-procedures, a direct cytotoxic agent is needed. In all colorectal CHPPC-studies MMC has been used, with or without addition of other drugs like cisplatin and etoposide. MMC is chosen because of its known activity in colorectal cancer,[125] its direct cytotoxic effect, the thermal enhancement of its activity[84,93] and penetration depth[51] and its favourable pharmacokinetics in CHPPC-procedures. The latter has been demonstrated in our and other pharmacokinetic studies.[51,88,93,95,127-129] The ratio of locoregional exposure to systemic exposure of MMC varied from 3 to 53 depending on the total dose administered, timing of administration and CHPPC-technique used.[100,126,128] During abdominal perfusion concentrations of MMC in perfusate are 11 to 133 times higher than in the peripheral blood.[88,127-129]

In a phase I trial the administration of TNF and cisplatin during CHPPC was studied in 27 peritoneal carcinomatosis patients, among whom 11 had colorectal cancer.[117] While intravenous delivery of effective tumoricidal doses of tumor necrosis factor (TNF) is limited by systemic toxicity, it might be an attractive agent for this locoregional treatment, due to its significant synergistic cytotoxic effect with hyperthermia, like in isolated limb perfusion for sarcoma. An almost 5000–fold higher intraperitoneal than systemic exposure was achieved during CHPPC and there was no operative or treatment-related morbidity observed.

Morbidity

This aggressive regional treatment is associated with significant morbidity, probably mainly associated with the extensive surgery needed. The mortality rate varies from 0% to 20%, regardless of the technique and indication

Table 5. Characteristics of drugs used in intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal origin.

- Active against colorectal cancer
- High molecular weight
- Direct cytotoxicity (no antimetabolites)
- Synergistic effect with hyperthermia

used.[98,99,102,103,106,110,114,115,121,122,130] Mortality seems to be related to greater age and higher intra-abdominal temperature (>41.5 °C).[106] Major complications from different techniques have been reported in up to 35% of cases and include anastomotic leak, bowel perforations, bile leak, pancreatitis, intra-abdominal bleeding, wound dehiscence, pulmonary embolism, renal failure and grade 3 and 4 hematological toxicity.[98,106,110,114,121,129,130] The latter is a result of the intraoperative chemotherapy and dose related, while renal failure is probably due to temporarily low renal perfusion state peroperatively in combination with absorption of nephrotoxic cytotoxic agents used like cisplatin and MMC.[129] Most complications, however, can be attributed to the extensive surgery performed, especially when the patient had had multiple operations before.[95] Duration of the operation, the number of peritonectomy procedures and resections and the number of suture lines are associated with morbidity.[130] In clinical randomized control studies on gastric cancer, hyperthermic intraperitoneal chemotherapy does not seem to be associated with increased anastomotic leakage.[90,97-101] The major intestinal complication after CHPPC remains

Table 6. Results of clinical phase I/II studies on cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal dissemination of colorectal or appendiceal carcinoma.

First author	Year	n	Site	FU in months	Overall survival	Periton. recurr.	Adj. syst. chemo.	Remarks
Nishimura[108]	1996	14	CR	12	1 yr 60%, 2 yrs 50%, 3 yrs 25%	-	no	2 pts. > 4 yrs recurrence free
Schneebaum[109]	1996	15	CR	15	-	-	no	unfavourable selection***, median response 6 months****
Fuzun[112]	1997	8	C	8	mean survival 12 months	50%	yes	short follow-up
Sugarbaker[113]	1999	161	A	-	2yrs 50%, 5 yrs 30%	-	no	EPIC or HIPEC + EPIC
Fujimara[118]	1999	14	CR	-	1 yr 51%, 2 yrs 21%	-	no	severe peritoneal dissemination, median survival 2 yrs
Loggie[114]	2000	38	CR	27*	1 yr 60%, 2 yrs 39%, 3 yrs 24%	-	no	
Loggie[114]	2000	22	A	27*	1 yr 74%, 2 yrs 52%, 3 yrs 52%	-	no	
Beaujard[115]	2000	21	CR	-	1 yr 50%	-	yes	median survival in limited and extensive dis. 26/7 months resp.
Cavaliere[116]	2000	14	CR	30*	2 yrs 64%	-		cytoreduction followed by CHPPC, EPIC or syst. chemotherapy
Piso[120]	2001	17	A	-	4 yrs 75%	-	no	only well-differentiated primary tumors
Witkamp[110]	2001	29	CRA	38	1 yr 82%, 2 yrs 45%, 3 yrs 23%	57%	yes	phase III study currently ongoing
Elias[121]	2001	27	CRA	52**	1 yr 85%, 2 yrs 70%, 3 yrs 53%	31%**	no	

n = number of patients, FU = median or mean follow-up period, periton. recurr. = peritoneal recurrence rate, C = colon, R = rectum, A = appendix, - = not reported, * = for the whole series of peritoneal carcinomatosis, not separately defined for colorectal/appendiceal cancer, ** = for all 64 patients treated by CHPPC or EPIC, *** = all patients had progression during prior systemic chemotherapy, **** = recurrence defined as elevated serum carcinoembryonic antigen (CEA) or on CT-scan, EPIC = early postoperative intraperitoneal chemotherapy, CHPPC = intraoperative continuous hyperhermic perfusion peritoneal chemotherapy, dis. = disease, resp. = respectively, syst. = systemic.

bowel perforation, which is probably caused by surgical trauma of the bowel surface combined with thermal and chemotherapeutic damage.[106] Prolonged ileus and gastric atonia are other common postoperative complications. In the few series concerning CHPPC for peritoneal seeding from colorectal or appendiceal origin, morbidity and mortality rates of 7-67% and 0-11% have been reported respectively.[106-110,112,115,120] These percentages, and also the kind of complications, are similar to those after CHPPC for other indications. These numbers appear similar to morbidity and mortality after palliative operations in patients with peritoneal carcinomatosis of colorectal origin. In conclusion, CHPPC for colorectal cancer is feasible and associated with an acceptable morbidity and mortality, rate.

Outcome

Fujimoto and colleagues[131] applied CHPPC with MMC limited to the pelvis as adjuvant treatment in 14 patients with resectable advanced rectal cancer, resulting in a low local recurrence rate. After a median follow-up of 17 months there was no recurrence in these 14 patients, while in a non-randomized control group of 12 patients 2 local recurrences occurred.

The results of phase I/II studies on aggressive cytoreductive surgery and CHPPC for peritoneal dissemination of colorectal cancer are summarized in table 6.[108-110,112-116,118,120,121] The 2-year survival rate varies from 40 to 70%. Sugarbaker from the Washington Cancer Institute, who is regarded as the pioneer of this method, has not reported separately his results from this approach for colorectal cancer. In his recent monograph on management of minimal residual disease of colon cancer,[132] he presented his clinical pathway used to treat patients with peritoneal carcinomatosis from colon cancer. Only patients with a limited extend of peritoneal involvement and for whom optimal surgical cytoreduction was obtained were selected for CHPPC and early postoperative intraperitoneal chemotherapy. The number of patients selected to be treated in this way and the follow-up period is not mentioned. For these patients 5-year survival rates of 20% to 50% were observed. In a recent report,[113] Sugarbaker reported 2- and 5-year survival rates of approximately 50% and 30%, respectively, for 161 patients treated by intraperitoneal chemotherapy for peritoneal surface spread of appendiceal mucinous adenocarcinoma. It remains unclear in this report how many of these patients were having a pseudomyxoma peritonei, traditionally associated with a better prognosis than the 'real' adenocarcinoma of the appendix, and how many were also treated by CHPPC instead of early postoperative intraperitoneal chemotherapy only. Piso et al.[130] reported a 4-year overall survival rate of 75% for 17 patients with appendiceal carcinoma and peritoneal carcinomatosis treated by cytoreductive surgery and CHPPC. However, only well-differentiated primary tumors were treated, making it assumable that also pseudomyxoma-like neoplasms were included. Therefore, these results of the two latter studies are difficult to interpret, which may explain the significantly increased survival rate in those groups of patients compared to other series. Besides low grade histology, optimal cytoreductive surgery and the preoperative absence of ascites are associated with significantly improved survival.[114,120]

CONCLUSIONS

Adjuvant 5-FU based early postoperative intraperitoneal chemotherapy is worth considering as a treatment option after resection of high-risk colorectal cancer, especially when tumor infiltration is through the entire bowel wall and exfoliation of malignant cells with peritoneal dissemination is likely. Meta-analysis of randomized trials demonstrates a positive impact on overall survival and regional tumor control.

In the treatment of peritoneal carcinomatosis so many adhesions are involved that postoperative intraperitoneal chemotherapy leads to inadequate exposure of the peritoneal surface. Intraoperative intraperitoneal chemotherapy results in a more uniform distribution of the cytotoxic drug throughout the abdominal cavity. In the therapeutic setting, patients with no gross or very small volume residual disease after cytoreductive surgery seem to benefit most from this approach. Intraperitoneal chemotherapy is unlikely to be beneficial in more bulky disease since drug penetration into larger tumor nodules is limited.

The results of phase II studies on aggressive cytoreductive surgery and CHPPC for peritoneal carcinomatosis from colorectal and appendiceal origin suggest that an increased median survival can be achieved with this treatment compared to palliative surgery and conventional systemic chemotherapy and the natural history. While long-term disease-free survival has been noted in some studies on intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal origin, in which the investigators have suggested that this survival is superior to that predicted by the natural history of the malignancies, it remains unknown what role intraperitoneal treatment played in the outcome. For example, patients selected for aggressive cytoreductive surgery and intraperitoneal chemotherapy may not be comparable

to other individuals with similar tumor load, making comparisons in the absence of controlled trials difficult. The performance status of individuals undergoing such aggressive multimodality treatment, a known important prognostic factor for survival in colon cancer, will almost certainly be superior to an unselected patient population with metastatic colon cancer. There is an enormous inter-individual variety in peritoneal tumor load, varying from some small superficial tumor nodules on the peritoneal surface next to the primary tumor site to a peritoneal cavity full of large invasive tumor deposits.

The natural history of this disease and the heterogeneity of the patients are such that comparison to historical controls is unreliable and only a randomized trial design will adequately answer the question whether regional treatment of patients with peritoneal dissemination of colorectal cancer actually prolongs survival. Results of a completed randomized trial from the Netherlands are to be expected soon.

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