REVIEW

Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis

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Abstract

This article is to offer a concise review on the use of cytoreductive surgery (CRS) plus intraperitoneal hyperthermic chemotherapy (IPHC) for the treatment of peritoneal carcinomatosis (PC). Traditionally, PC was treated with systemic chemotherapy alone with very poor response and a median survival of less than 6 mo. With the establishment of several phase Ⅱ studies, a new trend has been developed toward the use of CRS plus IPHC as a standard method for treating selected patients with PC, in whom sufficient cytoreduction could be achieved. In spite of the need for more high quality phase Ⅲ studies, there is now a consensus among many surgical oncology experts throughout the world about the use of this new treatment strategy as standard care for colorectal cancer patients with PC. This review summarizes the current status and possible progress in future.

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INTRODUCTION

The loco-regional progression of gastrointestinal and gynecological cancers usually result in peritoneal carcinomatosis (PC), which is characterized by the presence of tumor nodules of various size, number and distribution on the peritoneal surface, with very poor prognosis and a median survival of less than 6 mo[1-3]. The most widely accepted therapies for such PC are systemic chemotherapy, best support care and palliative treatment, without any hope of cure. Moreover, surgery alone can only remove the bulky visible tumor nodules. For the micrometastases, invisible free cancer cells and those tumor masses not suitable for resection, surgery can not achieve any effect. Therefore, neither surgery nor chemotherapy alone can make obvious positive impact on the survival and quality of life in patients with PC. In order to tackle this difficult problem, a new treatment modality called cytoreductive surgery (CRS) plus intraoperative peritoneal hyperthermic chemotherapy (IPHC) has been developed over the past two decades, which has the advantages of surgery to reduce the visible tumor burden and regional hyperthermic chemotherapy to eradicate micrometastses and free cancer cells[4]. Over the past decade, this treatment modality has gained increasingly wide acceptance in clinical practice and in some cancer centers in Europe, America, Japan and Australia, and has been adopted as the treatment of choice for PC from gastrointestinal tract or pelvic malignancies. This paper summarizes the biological basis, the indications and contraindications, the techniques, the efficacy and safety issues and future directions of this new treatment.

INCIDENCE, MORBIDITY AND MORTALITY OF PC

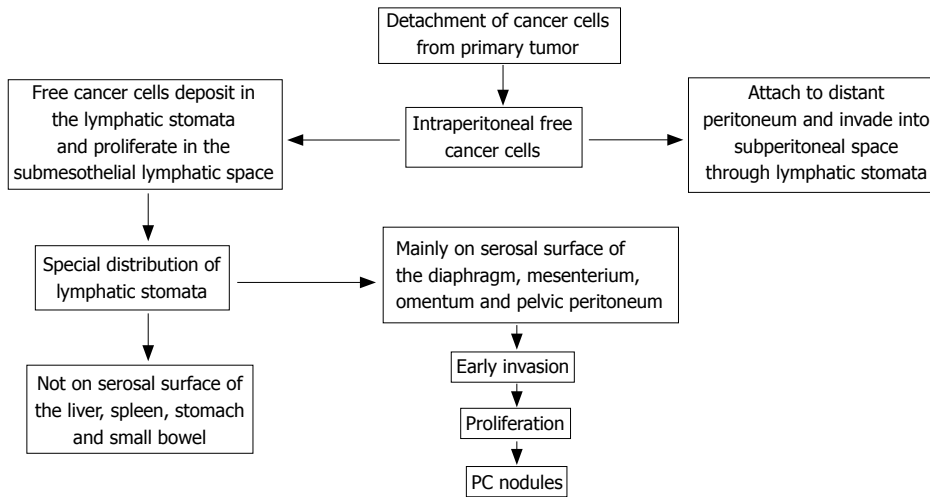PC is a direct consequence of loco-regional progression

of gastrointestinal and gynecological cancers including gastric cancer (GC), colorectal cancer (CRC), ovarian cancer (OC), appendiceal cancer and malignant peritoneal mesothelioma.

For GC, 10%-20% of patients being explored for potentially curative resection are found to have peritoneal seeding at the time of abdominal exploration. This occurs most frequently in patients with signet ring cell type of GC as opposed to intestinal type pathology[5]. Furthermore, peritoneal recurrence develops in 60% of patients with T3 or T4 tumor after curative resection[6]. In T3 or T4 tumor, invisible micrometastases are already present in the peritoneal cavity at the time of curative resection, and peritoneal recurrence is the only site of the first recurrence in 40%-60% of patients[7-9]. Therefore, peritoneal dissemination alone usually results in death of 20%-40% of patients with GC[10].

For CRC, peritoneal seeding of cancer cells leading to PC is rather common. It is estimated that, at the time of diagnosis, the peritoneal surface is already involved in 8%-15% of CRC cases, and that initial recurrence in the peritoneum occurs in up to 50% of patients after curative surgery[11-14]. In approximately 25% of patients with recurrent CRC, the peritoneal cavity seems to be the only metastatic site of the disease, even after a detailed diagnostic workup of the liver and lungs[15].

OC is another malignancy prone to peritoneal metastasis. About 50%-75% of women with OC will develop persistent or recurrent disease with a long survival rate in only 25% patients[16,17]. In about 82% of the cases, the recurrence is within the peritoneal cavity while in 12% it occurs in the retroperitoneal lymph nodes[18-20]. For early stage OC, the median recurrence time ranged between 11 mo and 29 mo with much more involvement of the pelvis or abdomen than retroperitoneal lymph nodes[21-28]. For advanced OC, if the initial treatment achieves meaningful clinical response, the median recurrence time ranges from 18 mo to 24 mo, again with peritoneal metastasis as the most common site[16,19,29-34].

MECHANISMS OF PC DEVELOPMENT

PC is formed through a multi-step process (Figure 1): (1) detachment of cancer cells from primary tumor.

The origin of PC in GC, for example, is considered to be the intraperitoneal free cancer cells, which are exfoliated from the serosal surface of the primary tumor; (2) intraperitoneal free cancer cells attach to the distant peritoneum, and invade into the subperitoneal space; (3) invasion into subperitoneal space; and (4) proliferation with vascular neogenesis[35,36].

Recent studies have revealed special anatomical basis for peritoneal metastasis. Yonemura et al[9,37] found special peritoneal lymphatic orifices, which are referred to as the lymphatic stomata and connect with subperitoneal lymphatic channel and milky spots. Milky spots are the minute organelles which contain lymphatic vessels, lymphocytes, and peritoneal macrophages. Milky spots distribute mainly on the greater omentum and pelvic peritoneum. Intraperitoneal free cancer cells specifically deposit in the lymphatic stomata and proliferate in the submesothelial lymphatic space. The lymphatic stomata showed special distribution on the peritoneal surface. Numerous stomata are detected on the undersurface of the diaphragm, small bowel mesentery, greater omentum, appendix epiploicae of the large bowel and the pelvic peritoneum. In contrast, there are no lymphatic stomata on the liver capsule, the surface of the spleen and the serosal surface of the small bowel and stomach. Accordingly, the serosal surface of these organs is involved only at the late phase of peritoneal dissemination.

CURRENT TREATMENT STRATEGIES AGAINST PC

For a long time, PC has been considered as a preterminal condition and treated with systemic chemotherapy alone with poor outcome; and the role of surgery is just palliative to relieve intestinal obstruction. But at least 1 phase III and many phase II studies have shown that the use of CRS with IPHC can improve survival for PC. Currently, such method of treatment has evolved into a novel approach for PC and might represent the standard care in selected patients (Figure 2)[38-40].

Rationale
Intraoperative use of chemotherapeutic agents to maximize

the efficacy of both surgery and chemotherapy has many advantages. First, surgery can separate the adhesions and remove the bulky tumor, leaving microscopic residual tumors much more susceptible to the killing effect of chemotherapeutic drugs. Second, intraperitoneal chemotherapy has distinct pharmaceutical advantages. In a recent phase I study by Morgan et al[41], 36 patients with PC of different origin were treated with intraperitoneal gemcitabine chemotherapy. It was found that the median peak peritoneal concentration was 1116 folds (range, 456-1886) higher than the peak plasma level. This could increase the local drug concentration, thus intensifying its direct antitumor effect while reducing the systemic adverse effects. Such preferential high concentration of drugs in the peritoneal cavity also occurs in many other drugs such as doxorubicin, melphalan, mitomycin C, cisplatin, gemcitabine, mitoxantrone, oxaliplatin, etoposide, irinotecan, paclitaxel, docetaxel, 5-fluorouracil, floxuridine and carboplatin[42]. Third, heat itself has direct detrimental effect on the growth of cancer cells. Cell membrane, cytoskeletons, synthesis of macromolecules, and DNA repair mechanisms are all affected by hyperthermia[38]. Temperature over 43℃ has direct cytostatic effect on human breast cancer cell line MCF-7, ovarian SKOV-3 and hepatocarcinoma HEpG2 cells[43]. Fourth, the synergistic effect of hyperthermia and chemotherapy has also been well-documented. It has been shown that hyperthermia increases the cytotoxicity of some chemotherapeutic agents[43-45]. Because of these advantages, CRS plus IPHC has been increasingly used in the treatment of PC from GC[46], malignant mesothelioma[47], appendiceal cancer[48], CRC and OC[49-60].

Indications, contraindications and patient selection

IPHC is commonly indicated for the treatment of PC with GC, CRC, appendiceal cancer, OC, peritoneal mesothelioma, pseudomyxoma peritonei and malignant ascites, if the patients can stand CRS and IPHC[38]. The contraindications are as follows: (1) patients are medically unfit to undergo the rigors of CRS and IPHC e.g. those with renal and myocardial impairments; (2) there is an extra-abdominal disease; (3) parenchymal hepatic metastases; (4) bulk retroperitoneal disease; (5) the peritoneal tumor is incompletely resected or can not be significantly reduced; and (6) patients aged over 70 years[38]. A clear preoperative staging of PC is necessary for such treatment. Preoperative abdominopelvic CT, MRI, positron emission tomography (PET) or PET/CT, or laparoscopy are adequate procedures[39].

Techniques

Complete CRS is vital in improving the survival of patients with PC, although in some patients with limited PC, partial removal of peritoneum is enough to eliminate macroscopic disease[61]. The goal of complete CRS is to remove all macroscopic peritoneal dissemination. Peritonectomy consists of two big surgical components (parietal and visceral peritonectomy). A midline incision extending from xiphoid process to pubis is sometimes necessary, complete parietal peritonectomy can be achieved by stripping off the parietal peritoneum at the abdominal incision, then
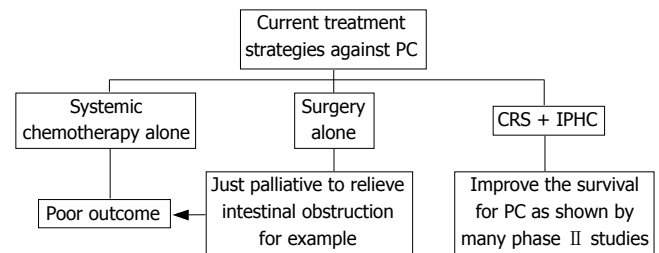

Figure 2 Rationale of CRS plus IPHC in treating PC.

ascending colon, spleen, pancreatic tail, and descending sigmoid colon are mobilized, and all peritoneum lining the lower abdominal wall and pelvis is removed. Visceral peritonectomy includes subtotal colectomy, omentectomy, partial gastrectomy, and resection of mesentery to the extent that they are involved[10].

It is mandatory to examine the greater omentum, undersurface of diaphragm and Douglas pouch as free cancer cells can lodge there due to presence of lymphatic stomata[62]. Micrometastasis on the preserved peritoneum can be managed by intraperitoneal chemotherapy, so complete cytoreduction includes the removal of peritoneum with gross nodules[10,61,62].

After finishing CRS, IPHC is initiated. It has been shown that hyperthermia augments the penetration of anticancer drugs[63], in addition to its synergistic cytotoxicity on cancer cells when combined with some chemotherapeutic drugs such as mitomycin C (MMC) and cisplatin[64]. It is performed either with open or closed techniques, with more advantages of the former due to uniform distribution of the chemotherapeutic agents within peritoneal cavity[10]. In either technique, large volume (5 L-10 L) of saline heated at 42℃-43℃ is introduced into the peritoneal cavity and circulated at a high flow rate of about 10 L/min[10]. The total dose of MMC and CDPP should be 30 mg and 300 mg, respectively with an optimal duration of 60-90 min[10].

ASSESSMENT OF COMPLETENESS OF CRS

There is agreement among many treatment centers that the extent of disease prior to CRS and the completeness of cytoreduction (CCR) score are the principal prognostic indicators for survival[14,38,66-85]. In CCR, the extent of residual disease after CRS is classified into 4 categories: CCR-0 indicating no visible residual tumor; CCR-1, residual tumor ≤ 2.5 mm in diameter; CCR-2, residual tumor between 2.5 mm and 2.5 cm; and CCR-3, residual tumor > 2.5 cm or confluence of disease present at any site[86]. But those with more diffuse disease (more than 2 quadrants) become worse no matter how good a cytoreduction procedure is. The understanding of a complete cytoreduction may vary according to the disease process, for example, in colorectal PC, complete cytoreduction needs a CCR-0 score[14,66-85] while in pseudomyxoma peritonei, a complete cytoreduction may involve both CCR-0 and CCR-1[39,87].

Table 1 The survival rates of CRS plus IPHC in patients with PC of different malignancies

Authors	Pts n	Year	Type of study	Tumor type	Drugs, temperature & duration	Median follow-up time	1 yr	2 yr	3 yr	4 yr	5 yr
Pilati et al[90]	34	2003	Phase II	Colon ca	MMC 26.2 mg (20.1-31.6 mg) CDDP 193.7 mg (170-241.1 mg), 41.5℃ (41.2℃-42.1℃), 90 min	14.5 mo (6-34 mo)	68	31	-	-	-
Glehen et al[81]	56	2003	Phase II	CRC, OC, GC, peritoneal Mesothelioma, Pseudomyxoma peritonei, and others	MMC 0.7 mg/kg (max dose 60 mg), CDDP 1 mg/kg (max dose 80 mg), 46℃-48℃, 90 min	544.4 d (133-1680 d)	-	R0: 79.0; R2: 44.7	-	-	-
Verwaal et al[67]	54	2003	Phase III	CRC	MMC 70 mg, 41℃-42℃, 90 min	21.6 mo	67	44	-	-	-
Witkamp et al[60]	29	2001	Phase I / II	CRC	MMC 35 mg/m², 40℃-41℃, 90 min	38 mo (26-52 mo)	82	45	23	-	-
Shen et al[84]	77	2004	Phase II	CRC	MMC 40 mg, 40.5℃, 120 min	15 m	56	-	25	-	17
Elias et al[91]	24	2004	Phase II	CRC	LOHP 460 mg/m² in 2 L/m², 43℃, 30 min	27.4 mo (18.3-49.6 mo)	83	74	65	-	-
Yonemura et al[92]	107	2005	-	GC	MMC 30 mg, CDDP 300 mg, etoposide 150 mg, 42℃-43℃	46 mo	-	-	-	-	6.7 all pts; 27 R0 pts
Yonemura et al[93]	48	2001	Randomized study	T2-T4 GC	MMC 30 mg, CDDP 300 mg, 42℃-43℃, 60 min	5.5 yr (2.4-10.8 yr)	-	-	-	-	61
Elias et al[94]	30	2006	Phase II	CRC	LOHP 460 mg/m² in 2 L/m² of iso-osmotic 5% dextrose, 43℃, 30 min	55 mo (24-80 mo)	97	73	53	49	-
Yan et al[75]	30	2006	-	CRC	-	12 mo	72	64	-	-	-
Glehen et al[78]	53	2004	Phase II	CRC	MMC 40-60 mg, 46℃-48℃, 90 min	60 mo	55	32	-	-	11
Helm et al[95]	18	2007	Retrospective review	Recurrent OC	CDDP 100 mg/m² or MMC 30-40 mg, 41℃-43℃, 90 min	16.2 mo (6-33 mo)	-	60	-	-	-
Deraco et al[96]	33	2004	phase II	Pseudomyxoma peritonei	CDDP 25 mg/m² per L plus MMC 3.3 mg/m² per L, 60 min, 42.5℃	28.6 mo (0.4-72 mo)	-	-	-	-	97
Cavaliere et al[97]	69	2003	Phase II	CRC	MMC	-	-	-	27	-	-
Glehen et al[66]	506	2004	Phase II	CRC	MMC/LOHP, 40℃-43℃, 30-90 min	53 mo	72	-	39	-	19
Verwaal et al[98]	117	2005	Phase II	CRC	MMC 35 mg/m², 40℃-41℃, 90 min	46 mo	75	-	28	-	19
Sugarbaker et al[72]	70	2006	Phase II	CRC	MMC	47 mo	88	-	44	-	32
Helm et al[99]	5	2007	Retrospective review	Recurrent endometrial ca	CDDP 100 mg/m², 41℃-43℃, 90 min	36 mo	80	80	80	80	-
Zanon et al[100]	25	2006	Phase II	CRC	MMC 15 mg/m², 42℃, 60 min	36 mo	64	40	-	-	-
Piso et al[101]	19	2004	-	OC	CDDP 75 mg/m², or mitoxantrone 15 mg/m², 41.5℃, 90 min	-	-	-	-	-	15
Roviello et al[102]	59	2006	-	OC, CRC, GC, Pseudomyxoma, Mesothelioma	MMC 25 mg/m², CDDP 100 mg/m². (LOHP 460 mg/m² in 4 pts with colorectal PC), 41℃-43℃, 60 min	25 ± 21 mo	-	-	-	-	50.8

GC: Gastric cancer; CRC: Colorectal cancer; OC: Ovarian cancer; MMC: Mitomycin C; CDDP: Cisplatin; LOHP: Oxaliplatin.

EFFICACY AND BENEFIT OF CRS PLUS IPHC

It is now clear that CRS plus IPHC improves both the quality of life especially in patients with malignant ascitis[15,103,104], and the survival[15,67]. The results of the most significant studies about the survival rates are summarized in Table 1, which supports the use of this new modality as standard care.

ADVERSE EVENTS OF IPHC

IPHC is associated with a high morbidity rate ranging from 27% to 56%[38]. The adverse events can be classified into CRS-related and chemotherapy-related morbidity[15]. Surgery-related adverse events are abscess, intestinal perforation, fistula, prolonged ileus, bile leakage, pancreatitis, pneumonia, deep vein thrombosis, pulmonary emboli, cardiac insufficiency and cerebral infarcts[11,38].

Multivariate analysis demonstrated that adverse events are related to the stage of PC, the operation duration, the number of anastomoses, and blood loss[38,88].

Main chemotherapy-related side effects are bone marrow suppression and renal insufficiency mostly with use of cisplatin[11]. The mortality rate for IPHC ranges between 0% and 11%, and the most common causes of death are bowel perforation, bone marrow suppression, respiratory failure, methicillin resistant staphylococcus aureus infection, and pulmonary embolism[38].

In spite of the above morbidities, such modality remains the suitable one if not the best at present because the patients with PC might get worse without it as systemic chemotherapy or surgery alone is associated with much poorer outcome. With careful and accurate selection of patients, excluding those who are unfit, it is possible to reduce the morbidities of CRS + IPHC and yield a significantly favorable impact on improving survival of the patients.

FUTURE DIRECTIONS

Recently a panel of 55 experts in PC has reached the consensus, which stated that systemic treatment alone may be no longer appropriate for patients with limited PC from a primary or recurrent colon cancer. CRS plus IPHC as a new treatment strategy have clear advantage in this setting[89]. Such procedure has been approved by the surgical oncology experts on PC from North America, France, Italy, Germany, Holland, Spain and Australia. The consensus also indicated that patients who have isolated PC and are likely to receive a complete cytoreduction, as determined by preoperative CT scans, should undergo CRS; and if complete cytoreduction is achieved, intraperitoneal hyperthermic MMC should be given (at 15-35 mg/m^2, 39℃-42℃, for 60-120 min, either by closed or open instillation), followed by best adjuvant systemic chemotherapy[65].

Several issues have been discussed about the future of this treatment strategy, one of which is how to make such therapy standardized and available to large numbers of patients. The operative procedures required for aggressive cytoreduction are lengthy, challenging and morbid and use a great deal of hospital, blood bank, and operational theater resources[38]. Even though this treatment strategy has been confirmed to be effective in some centers, there is only one randomized clinical trial to definitely establish its efficacy in terms of improving the survival and the quality of life of patients with colorectal PC[39,67]. Currently, a large scale prospective multi-center phase II study using CRS and IPHC with MMC followed by modern adjuvant systemic chemotherapy for patients with isolated colorectal PC is in progress. This study involves 66 peritoneal surface malignancy surgeons from 46 institutions in 16 countries. Once completed, this study will provide better evidence as to the efficacy of this treatment modality[89].

It is clear that CRS plus IPHC is not indicated for all patients with PC, and the results achieved by international experts in this field may not be replicated in routine clinical practice. Patients with good performance status, low volume of peritoneal disease, and absence of extra-abdominal metastases are more likely to benefit from the combined treatment. This means early diagnosis, early referral to specialist peritonectomy centers for staging, and prompt intervention are keys to successful management. Only by collaborative efforts from medical oncologists, surgical oncologists, and peritoneal surface malignancy treatment centers can such result be achieved[39].

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