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Scientific Research

Intraperitoneal Chemotherapy for Gastric Cancer with Peritoneal Carcinomatosis: Is HIPEC the Only Answer?

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Abstract

Gastric cancer with peritoneal carcinomatosis is notorious for its dismal prognosis. While the pathophysiology of peritoneal dissemination is still controversial, the rapid downhill course is universal. Patients usually suffer abdominal distension, intestinal obstruction and various complications before they succumb after a median of 3 - 6 months. Although not adopted in most international treatment guidelines, intraperitoneal chemotherapy has growing evidence compared with conventional systemic chemotherapy for the treatment of peritoneal carcinomatosis. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is well-established for clinical benefit but is technically demanding with substantial treatment-related morbidities and mortality. On the other hand, normothermic intraperitoneal chemotherapy in the form of bidirectional neoadjuvant treatment is promising with various newer chemotherapeutic agents. Regardless of the treatment technique applied, the essential element of success is meticulous patient selection and availability of expertise. Future direction is along the line of personalized treatment with the application of translational science.

Keywords

Gastric Cancer, Peritoneal Carcinomatosis, Hyperthermic Intraperitoneal Chemotherapy (HIPEC), Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS), Cytoreductive Surgery

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1. Introduction

1.1. Epidemiology

Gastric cancer is the fifth most common malignancy in the world and almost one million new cases were estimated to have occurred in 2012. About half of the cases occurred in Eastern Asia and a male-predominance was observed [1]. Peritoneal carcinomatosis (PC) is one of the most dismal manifestations of advanced gastric cancer. In more than 20% of patients, early peritoneal dissemination, in the form of either positive cytology or PC, was detected at presentation [2] and the likelihood increased with the extent of serosal invasion [3]. On the other hand, involvement of the peritoneum as a component of first recurrence was reported to be as high as 10% - 50% even after standard D2 lymph node dissection and adjuvant chemotherapy [4]-[6]. Patients with PC not only have a poor quality of life due to various complications including ascites and intestinal obstruction but also have a universally grave prognosis. According to the multicenter prospective EVOCAPE I study, the median overall survival (OS) in gastric cancer patients with PC was 3.1 months substantially worse than the 5.2 months in colorectal cancer patients with PC [7].

1.2. Staging

Proper staging workup is essential for assessing the extent of disease and selection of patients for aggressive treatment. Contrast-enhanced CT is regarded as the fundamental imaging modality for PC [8]. The reported sensitivity ranged from 60% - 90% depending on the quality of CT, size of the tumor nodules and its location in the peritoneal cavity. The presence of ascites and peritoneal thickening with or without enhancement are the commonest CT features. PET provides complementary staging information to CT with high sensitivity except in signet-ring cell carcinoma which has generally low maximum Standardized Uptake Value [9]. On the other hand, the high physiologic uptake in the stomach, bowel and urinary tract may lead to false-positivity. Diagnostic laparoscopy provides direct visualization of the peritoneal cavity and allows biopsy of lesions. However, it is invasive and may be technically difficult in patients with prior extensive surgery. In addition, it does not allow examination of the retroperitoneal region [8].

The peritoneal cancer index (PCI) is widely-adopted for the staging of PC. The peritoneal cavity is divided into 13 regions and a lesion size score (LS) is given to the largest tumor deposit within each region: LS 0 for no tumor seen, LS 1 for tumor up to 0.5 cm, LS 2 for tumor up to 5 cm and LS 3 for tumor >5 cm or confluence. The PCI is the sum of LS in all regions examined and it ranges from 0 to 39 [10]. Intraoperatively, the completeness of cytoreduction (CC) score is used to assess whether a cytoreductive surgery is complete. CC-0 indicates that there is no residual peritoneal seeding within the operative field and CC-1 for nodules <2.5 cm. CC-2 and CC-3 denote residual tumor 2.5 - 5 cm and >5 cm, respectively. CC-0 and CC-1 are regarded as complete cytoreduction. In general, both PCI and CC scores are important prognostic factor for patients with PC [11].

1.3. Recommendations from Major Treatment Guidelines

Palliative chemotherapy is recommended for patients with good performance status and adequate organ functions. Platinum-based chemotherapy doublet is favored in the East while chemotherapy triplet with an anthracycline or a taxane is commonly used in the West. For HER2-positive tumors, trastuzumab should be considered [12]. So far, no specific recommendation is given for a different treatment strategy for patients with PC and intraperitoneal chemotherapy is not discussed in any of the treatment guidelines of the National Comprehensive Cancer Network, the European Society for Medical Oncology and the Japanese Gastric Cancer Association [13]-[15]. As such, an appreciable gap exists between clinical practice and best available evidence regarding the optimal treatment of PC. This article serves to review current evidence and explore future directions in the treatment of this distinctive entity.

2. Intraperitoneal Chemotherapy (IPC) Overview

Transcoelomic spread of the cancer cells is the principle cause for PC and is independent of the hematological and lymphatic spread in systemic dissemination. Intraperitoneal administration of chemotherapy allows dose intensification since the peritoneal permeabilities of several hydrophilic chemotherapeutic agents are considerably less than the plasma clearance of the same agents [16]. As a result, there is higher drug concentration in the pe-

ritoneal cavity compared with systemic circulation and produce local cancer cell killing while minimizing systemic toxicity. In a recent metaanalysis that included 2145 patients in twenty prospective randomized controlled trials, surgery and IPC improved 1-, 2- and 3-year mortality rate (Odds Ratio = 0.31, 0.27 and 0.29, respectively) when compared to surgery alone in advanced gastric cancer [17]. The overall recurrence, peritoneal recurrence and hematogenous metastatic rates were also improved (Odds Ratio = 0.46, 0.17 and 0.63, respectively) at the price of increasing the morbidity rate (Odd Ratios = 1.82). Although any form of IPC was allowed for inclusion in the metaanalysis, twelve of the twenty studies utilized hyperthermic intraperitoneal chemotherapy (HIPEC) and cisplatin, mitomycin C and 5-FU were the commonly used chemotherapy.

2.1. Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

HIPEC combines the dose intensity advantage of IPC and the direct cytotoxic effect of hyperthermia. Patients with PC usually receive HIPEC at a temperature of 40˚C - 45˚C over 30 - 90 minutes in the operating theatre after cytoreductive surgery. Hyperthermia exhibits a selective cell-killing of malignant cells, potentiates the cytotoxic effect of chemotherapeutic agents and enhances tissue penetration of the agents [18]. It has been used with promising result in PC from various cancers including ovarian, colorectal, peritoneal mesothelioma and pseudomyxoma peritoneii [19]. Among the treatment of PC from gastrointestinal cancers, the result in colorectal cancer was favorable. Verwaal *et al.* reported the long-term follow-up result of a randomized trial that compared systemic chemotherapy alone with cytoreduction followed by HIPEC and systemic chemotherapy [20]. The median disease-specific survival was significantly improved from 12.6 months in the control arm to 22.2 months in the HIPEC arm ($p = 0.028$). In the subgroup of patients who had a R1 resection, long-term survival is possible with a 5-year survival rate of 45%. The result in gastric cancer echoes with similar degree of benefit. In a systemic review performed by Gill *et al*. that included studies of gastric cancer with PC treated by cytoreductive surgery and HIPEC, the median overall survival (OS) was 7.9 months but increased to 15 months in those with CC score 0 or 1 [21]. Overall rate of mortality and morbidity was 4.8% and 21.5%, respectively. The commonest complications reported were abscess, fistula and anastomotic leak.

Although the morbidity and mortality associated with HIPEC are substantial, studies have shown that the quality of life of patients was comparable to other cancer patients and in general returned to baseline at up to 1 year after treatment despite an initial drop in quality of life [22]-[24]. Nevertheless, the importance of the availability of expertise should not be overemphasized. Kusamura *et al*. reviewed 462 cases of cytoreductive surgery and HIPEC procedure performed from 1995 to 2012 of the peritoneum surface malignancy program in the Istituto Nazionale dei Turmori in Milan [25]. A steep learning curve was shown and approximately 140 to 150 procedures are required to assure adequate radicality of resection and acceptable safety. Similarly, 80 to 100 cases were necessary to assure short-term prognostic gains in rare peritoneal surface malignancies. Besides expertise, appropriate facilities are also critical. High-voltage electrosurgery is used for dissection, resection and electroevaporation of tumor nodules during cytoreductive surgery and excessive smoke generated from the extensive dissection and lengthy surgery pose potential health hazard. On the other hand, inhalation of chemotherapy aerosols or vapors as well as direct contact with the chemotherapeutic agents are additional health concerns, especially in those who practice open method of HIPEC [26]. Stringent protective measures should be followed to minimize the mentioned hazards.

2.2. Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Although HIPEC has encouraging efficacy, the associated morbidity and mortality as well as the demand on expertise and facilities all limit its availability worldwide. Recently, the concept of bidirectional chemotherapy using both intraperitoneal and systemic chemotherapy in the neoadjuvant setting has gained much attention. Taxanes such as paclitaxel and docetaxel are active against gastric cancer. Their remarkably high peritoneal/plasma AUC ratio as a result of the high molecular weight makes them ideal for intraperitoneal administration [27]. **Table 1** summarizes studies that used taxanes in NIPS. Yonemura *et al*. first tested the feasibility of NIPS in 79 gastric cancer patients with PC using oral S-1, intraperitoneal docetaxel and cisplatin [28]. Sixty-three percent of patients had their peritoneal cytology turned negative and 78% of patient who underwent laparotomy had complete cytoreduction. No treatment-related death was reported. Yonemura *et al*. subsequently reported the result of the same NIPS regimen in another 96 patients with PC [29]. Patients underwent cytoreductive surgery, gastrectomy and D2 dissection after two cycles of NIPS, the rate of negative cytology and complete

Table 1. Clinical outcomes of taxane-based NIPS.

Author, Year	N	Chemotherapy	Gastrectomy Rate	MST (Months)	1-Year Survival	Most Frequent G3 Toxicity
Paclitaxel						
Kitayama, 2014 [32]	64	IP Paclitaxel + IV Paclitaxel + Oral S-1	53%	26.4	82%	NR
Yamguchi, 2013 [33]	35	IP Paclitaxel + IV Paclitaxel + Oral S-1	60%	17.6	77.1%	34% (Neutropenia)
Kitayama, 2012 [34]	100	IP Paclitaxel + IV Paclitaxel + Oral S-1	52%	23.6	80%	36% (Neutropenia)
Ishigami, 2012 [35]	40	IP Paclitaxel + IV Paclitaxel + Oral S-1	NR	22.5	78%	38% (Neutropenia)
Docetaxel						
Canbay, 2014 [36]	194	IP Docetaxel + IP Cisplatin + Oral S-1 followed by CRS + HIPEC	78%	15.8	66%	NR for NIPS
Fushida, 2014 [37]	39	IP Docetaxel + Oral S-1	36%	16.2	70%	19% (Anorexia)
Yonemura, 2012 [29]	96	IP Docetaxel + IP Cisplatin + Oral S-1	70%	14.4 (all) 21.1 (CC-0)	61% (all)	3.1% (Fatigue)
Fujiwara, 2012 [31]	18	IP Docetaxel + Oral S-1	89%	24.6	76%	6% (Neutropenia)
Yonemura, 2009 [28]	79	IP Docetaxel + IP Cisplatin + Oral S-1	38%	20.4 (CRS)	87.4% (CRS)	3.8% (Derange Renal Function)

Abbreviations: IP: Intraperitoneal; IV: Intravenous; NR: Not Reported; CRS: Cytoreductive Surgery; CC: Completeness of Cytoreduction.

pathological response of PC were 69% and 36.8%, respectively. Fujiwara *et al*. enrolled 25 treatment-naïve gastric cancer patients with either positive cytology or PC to NIPS that comprised intraperitoneal mitomycin C and cisplatin followed by two cycles of intravenous docetaxel, 5-FU and cisplatin [30]. Radiological response was seen in 59% of patients while 56% of patients become negative in peritoneal cytology and the median OS was 16.7 months. In another phase II study by the same study team, 18 patients with positive peritoneal cytology or PC were given two cycles of oral S-1 and intraperitoneal docetaxel [31]. Gastrectomy with lymph node dissection but not peritonectomy was performed for those without gross PC post-NIPS. Peritoneal cytology turned negative in 78% of cases and 62.5% of patients with measurable disease showed major response by RECIST criteria. The median OS was 24.6 months and 1-year survival was 76%. Treatment was well-tolerated without grade 4 or above toxicity. In short, NIPS achieves high rate of response and favorable survival outcomes. Results are reproducible and treatment is well-tolerated. **Table 2** shows the comparison between HIPEC and NIPS.

3. Target Therapy

3.1. Catumaxomab

Catumaxomab is the only licensed target therapy for the treatment of malignant ascites so far. It is a trifunctional non-humanized monoclonal antibody with two different antigen-binding sites, one directing at the epithelial tumor cells via the epithelial cell-adhesion molecule (EpCAM) and another directing at the T-cells via CD3 molecule, and a functional Fc domain. The functional Fc domain serves to activate Fcγ-receptor I-, IIa- and III-positive accessory cells. Thus, catumaxomab works as a locoregional immunotherapy against EpCAM+ tumor cells in the peritoneal cavity [38]. In the landmark phase II/III trial that randomized cancer patients with recurrent symptomatic malignant ascites who were resistant to conventional chemotherapy into paracentesis or paracentesis with intraperitoneal infusion of catumaxomab, the puncture-free survival was significantly increased with catumaxomab (46 days vs 11 days, HR 0.254; $p < 0.0001$) [39]. The most common catumaxomab-related adverse events were cytokine release-related symptoms (pyrexia, nausea and vomiting) and abdominal pain which were largely mild to moderate and reversible. In addition, treatment with catumaxomab was shown to de-

Table 2. Comparison between HIPEC and NIPS.

	HIPEC	NIPS
Timing	Intraoperative	Neoadjuvant
Intraperitoneal Chemotherapy	Cisplatin or Mitomycin-C or Oxaliplatin or Doxorubicin	Paclitaxel or Docetaxel
Intraabdominal Temperature	40˚C - 45˚C	Body Temperature
Systemic Chemotherapy	Yes or No	Yes
Morbidity	High-Intermediate	Intermediate
Mortality	Yes	No
Expertise	High	Low
Efficacy	High	High
Level of Evidence	Intermediate	Low
Capital Investment	High	Low
Health hazard	Potential	Minimal

lay deterioration in quality of life [40]. To date, catumaxomab was studied in the adjuvant treatment of patient with completely resected gastric cancer with serosa infiltration (NCT00352833) and in those who have received neoadjuvant chemotherapy (NCT00464893). Both studies have been completed and the results are awaited. There are ongoing studies to evaluate the combination of catumaxomab with complete cytoreduction in the palliative setting (NCT01784900) and the combination catumaxomab with systemic chemotherapy in the induction setting (NCT01504256) for patients with PC from gastric cancer. The result of these studies will expand the indications of catumaxomab in gastric cancer.

3.2. Trastuzumab

Trastuzumab is a humanized monoclonal antibody against human epidermal growth factor receptor 2 (HER2). In the TOGA study, trastuzumab in addition to chemotherapy significantly improved the OS of patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer [12]. Bozzetti *et al.* has shown that there is high concordance rate of HER2 status around 95% - 98% between the primary gastric tumor and the metastases [41]. Thus, intraperitoneal administration of trastuzumab to augment the treatment efficacy will be a logical assumption. So far, there is only one case report on the use of intraperitoneal trastuzumab [42]. A phase I dose-escalating study is ongoing on the intraperitoneal use of radiolabelled trastuzumab in HER2 expressing tumors with predominantly intra-abdominal disease (NCT01384253).

3.3. Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). VEGF is responsible for angiogenesis and vascular permeability which in turn enhance PC and its associated ascites. Preclinical model has shown that bevacizumab might be effective for treatment of PC from gastric cancer [43]. El-Shami *et al*. has reported the efficacy of a cohort of nine patients with refractory ascites due to various solid tumors who were treated by intraperitoneal bevacizumab [44]. However, there is no ongoing study of its use in patients with gastric cancer.

Current studies on intraperitoneal chemotherapy for gastric cancer are shown in **Table 3**.

4. Conclusion

The treatment of gastric cancer with PC is evolving and the use of intraperitoneal chemotherapy has improved the outcomes of this group of patients. While HIPEC benefits a selected group of patients in the presence of expertise, NIPS offers less technically demanding alternatives with lower morbidity and mortality. Catumaxomab is just the beginning of personalized medicine in the treatment of PC and more translational studies have

Table 3. Current clinical trials of intraperitoneal chemotherapy.

	Phase	Primary endpoint	Major eligibility criteria	Chemotherapy (intraperitoneal)	Chemotherapy (systemic)	Status
Adjuvant						
NCT00992199	II	Rate of peritoneal metastasis	T3-4NxM0	Cisplatin and 5FU	Not specified	Unknown
NCT00858338	II	Toxicity	IB-IVM0	Floxuridine	5-FU and concurrent radiotherapy	Completed
NCT00006038	II	Efficacy and toxicity	T2N1-2M0 or T3-4NanyM0	Floxuridine and leucovorin	Docetaxel, cisplatin and 5-FU	Completed
NCT00002783	II	Efficacy and toxicity	II-IVM0	Floxuridine and leucovorin	Cisplatin and 5-FU	Completed
NCT00004103	II	RR and TTF	IB-IVM0	Floxuridine and cisplatin	Cisplatin and irinotecan	Completed
NCT01683864	II/III	PC free survival	T2-4Nany and Pcyt+	MMC and cisplatin (hyperthermic)	No	Recruiting
NCT02205008	III	RFS	Suspicious of serosal invasion	MMC and 5-FU	S-1	Recruiting
NCT01882933	III	OS	T3/4, N+ or Pcyt+	Oxaliplatin (hyperthermic)	No	Recruiting
Palliative						
NCT02024841	I	MTD and RD	Primary gastric cancer + PC or Pcyt+	Docetaxel	Cisplatin and S-1	Recruiting
NCT01525771	I/II	MTD in phase I; PFS at 6months in phase II	PC or Pcyt+	Docetaxel	Cisplatin and capecitabine	Ongoing
NCT01379482	II	OS	Primary gastric cancer + PC	Cisplatin and doxorubicin (Hyperthermic)	FP-based	Completed
NCT01854255	II	CBR	PC	Cisplatin and doxorubicin (pressurized aerosal)	No	Recruiting
NCT02092298	II	OS	PC or Pcyt+	MMC, cisplatin and sodium thiosulfate	No	Recruiting
NCT01739894	II	OS	PC or Pcyt+	Paclitaxel	Oxaliplatin and capecitabine	Recruiting
NCT01471132	II	OS	PC or Pcyt+	Oxaliplatin and paclitaxel (hyperthermic)	No	Recruiting
NCT01342653	II	DFS	PC	Docetaxel and cisplatin MMC and doxorubicin (hyperthermic)	5-FU, docetaxel and cisplatin	Recruiting
NCT01784900	II	PFS	PC and CCR	Catumaxomab	No	Recruiting
NCT01504256	II	Rate of mCR of PC	PC	Catumaxomab	5-FU, oxaliplatin and docetaxel	Recruiting
NCT02158988	III	OS	PC	MMC and cisplatin (hyperthermic)	Epirubicin, oxaliplatin and capecitabine +/− trastuzumab	Recruiting

Abbreviations: 5-FU: 5-Fluorouracil; RR: Response Rate; TTF: Time to Treatment Failure; PC: Peritoneal Carcinomatosis; Pcyt+: Peritoneal cytology positive; MMC: Mitomycin C; MTD: Maximum Tolerated Dose; RD: Recommended Dose; PFS: Progression Free Survival; OS: Overall Survival; FP: Fluoropyrimidine; CBR: Clinical Benefit Rate; DFS: Disease Free Survival; CCR: Complete Cytoreduction; mCR: Macroscopic Complete Response.

to be done in deciphering the biology of this distinct disease entity. Ongoing studies that apply novel agents, techniques and concept will add on to the armamentarium against PC.

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